IN THE UNITED STATES PATENT AND TRADEMARK OFFICE #13

In re	:	U.S. Patent No. 4,260,769
Issued	:	April 7, 1981
Patentee	:	Valentino J. Stella and Kenneth B. Sloan
For	:	5,5-Diphenylhydantoins

Box Patent Ext.
Commissioner of Patents and Trademarks
Washington, D.C. 20231

TRANSMITTAL OF AN APPLICATION

FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for a product approved on **August 5, 1996** .

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

[X] A prescribed fee in the amount of $1,060.00 is required for the application presented.
Please charge Deposit Account No. 23-0455 in the amount of the prescribed fee above, or such greater or lesser amount of excess fees for claims as the Commissioner determines is required by law. This letter is submitted in triplicate for deposit account purposes.

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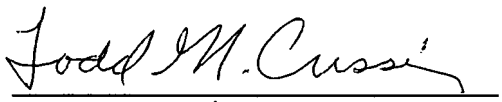
23149 111 1,060.00CH

Respectfully submitted,



September 27, 1996
Date

Todd M. Crissey
Registration No. 37,807
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (313) 996-7530

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 with Declaration and attachments thereto.

[X] A certified DUPLICATE APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] This Transmittal Form in triplicate for deposit account purposes.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent No. 4,260,769
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ORIGINAL APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Number: 4,260,769

Patentees: Valentino J. Stella and Kenneth B. Sloan

Issue Date: April 7, 1981

Title: 5,5-Diphenylhydantoins

APPLICATION FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. §156

Box Patent Ext.
Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to §201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains, New Jersey, 07950, agent of Merck & Company, the assignee of record, hereby requests an extension of the patent term of United States Patent No. 4,260,769.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740.

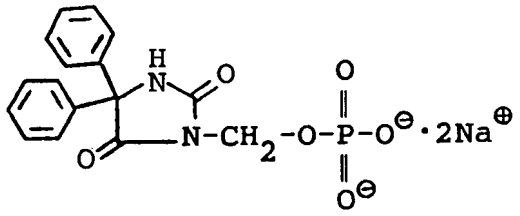
(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure characteristics:

The approved product is Cerebyx® (fosphenytoin sodium). The active ingredient in Cerebyx® is fosphenytoin sodium. Cerebyx® is for parenteral administration.

Chemically, Cerebyx® is 5,5-diphenyl-3-[(phosphonooxy)-methyl]-2,4-imidazolidinedione sodium salt; or 3-phosphoryl-oxymethyl-5,5-diphenylhydantoin (see USAN 1996, page 314).

Cerebyx® is also known as CI-982 and ACC-9653.

Cerebyx® has the structural formula



Cerebyx® (fosphenytoin sodium) is a pharmaceutical for parenteral use; see the sections titled DESCRIPTION and DOSAGE and ADMINISTRATION in Exhibit 1 (PACKAGE INSERT) which is the Product Information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under §505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Cerebyx® (fosphenytoin sodium) was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FFDCA on August 5, 1996; see Exhibit 2 (APPROVAL LETTER).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in Cerebyx® (fosphenytoin sodium) is fosphenytoin sodium. Fosphenytoin sodium has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on August 5, 1996, and the last day within the sixty day period permitted for submission of an application for extension of the patent is October 3, 1996. The date of submission of the present application is no later than October 3, 1996, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NUMBER:	4,260,769
INVENTORS:	Valentino J. Stella and Kenneth B. Sloan
Issue Date:	April 7, 1981
Expiration Date:	April 7, 1998

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,260,769 is attached as Exhibit 3 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

No disclaimer, certificate of correction or reexamination certificate has been issued. No maintenance fee is required.

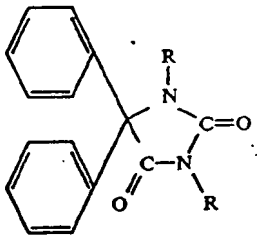
(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

The patent claims the approved product Cerebyx® (fosphenytoin sodium) in claims 1, 2 and 3.

Claims 1-3 are set forth below:

Claim 1.

A 5,5-diphenylhydantoin compound having the structural formula:



wherein each R is independently selected from the group consisting of hydrogen and $-CH(R_1)-O-P-(O)(OH)_2$, wherein R_1 is selected from the group consisting of hydrogen and C_1-C_7 straight or branched chain alkyl; with the proviso that the R's cannot simultaneously be hydrogen; or the pharmaceutically acceptable acid addition or basic salts, C_1-C_4 alkylhalide quaternary salts or N-oxide thereof.

Claim 2.

The compound as defined by claim 1, wherein either R is hydrogen, with the other being $-CH(R_1)-O-P(O)(OH)_2$.

Claim 3.

The compound as defined by claim 1, same being 3-phosphoryloxymethyl-5,5-diphenylhydantoin.

With regard to claim 1, the approved product Cerebyx® is covered when one R group is hydrogen and the other R group is $-CH(R_1)-O-P-(O)(OH)_2$ and R_1 is hydrogen.

With regard to claim 2, one R is defined as hydrogen and the other is defined as $-CH(R_1)-O-P(O)(OH)_2$. Cerebyx® is covered by claim 2 when R_1 is hydrogen.

Claim 3 claims the approved product Cerebyx®.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

On March 31, 1986, American Critical Care, the then patent owner, submitted to the Food and Drug Administration a "Notice of Claimed Investigational Exemption for a New Drug" (IND) fosphenytoin sodium (ACC-9653). A copy of this letter is submitted herewith as Exhibit 4 (IND SUBMISSION LETTER).

The IND was assigned number 28,217. The IND became effective on May 4, 1986, which is thirty days after receipt of the IND by the FDA; see Exhibit 5 (IND ACKNOWLEDGMENT LETTER) attached hereto. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1) as May 4, 1986.

On July 14, 1994, a new drug application (NDA 20-450) was submitted under §505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and §314.50 of Title 21 Code of Federal Regulations for Cerebyx® (fosphenytoin sodium) by the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company. A copy of the cover letter attached to the NDA of July 14, 1994, is submitted herewith as Exhibit 6 (NDA SUBMISSION LETTER).

By letter dated September 12, 1994, the FDA indicated that the NDA submitted on July 14, 1994, was not acceptable for filing.

The NDA was revised and resubmitted on February 22, 1995, under §505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and §314.50 of Title 21 Code of Federal Regulations for Cerebyx® (fosphenytoin sodium) by the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company. A copy of the cover letter attached to the February 22, 1995, NDA submission is attached as Exhibit 7 (NDA RESUBMISSION LETTER).

This resubmitted NDA was approved on August 5, 1996. Attached as Exhibit 2 (APPROVAL LETTER) is a copy of a letter dated August 5, 1996, from the FDA to Warner-Lambert Company approving the NDA for Cerebyx® (fosphenytoin sodium).

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. §156(g)(1), August 5, 1996, is the date of the first approval of fosphenytoin sodium, which is the active ingredient in Cerebyx®.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), an IND for Cerebyx® was submitted March 31, 1986, which became effective on May 4, 1986. The studies under the IND are summarized in the attached Exhibit 8 (IND LOG)*. These studies were used to support NDA 20-450 submitted by Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company on July 14, 1994, and revised and resubmitted on February 22, 1995.

Subsequent to the submission of the NDA, WARNER-LAMBERT COMPANY had numerous contacts and meetings with the FDA with respect to the application and these are summarized in the attached Exhibit 9,* (NDA LOG).

* Confidential and non-relevant material has been redacted.

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension Under 35 U.S.C. §156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and §156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here:

(1) The statutory term of U.S. Patent No. 4,260,769 expires on April 7, 1998. This Application has,

therefore, been submitted before the expiration of the patent term. In addition, there is no required maintenance fee because the patent was filed before the law requiring maintenance fees was effected.

(2) The term of this patent has never been extended.

(3) This Application is submitted by Warner-Lambert Company as agent for the owner of record, Merck & Company. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on the date, August 5, 1996, that the product received permission for marketing under the Federal Food, Drug and Cosmetic Act and contains the information required under 35 U.S.C. §156(d).

A copy of the letter from Merck & Company giving Warner-Lambert Company the right as agent to file this Application for Extension of Patent Term is attached as Exhibit 10 (AGENCY LETTER).

(4) As evidenced by the August 5, 1996, letter from the FDA, Exhibit 2, (APPROVAL LETTER) the product was subject to a regulatory review period under §505(b)(1) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of Cerebyx® (fosphenytoin sodium) after regulatory review under §505(b)(1) is the first permitted commercial marketing of fosphenytoin sodium. This

is confirmed by the absence of any approved new drug application under which fosphenytoin sodium could be commercially marketed prior to August 5, 1996.

Statement as to Length of Extension Claimed In Accordance With 37 C.F.R. §1.775

The term of U.S. Patent No. 4,260,769 should be extended for a period of 1826 days to April 7, 2003.

The period of extension is determined in accordance with 35 U.S.C. §156 and follows the format set forth in 37 CFR §1.775(c) and (d).

37 CFR §1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. §156(g)(1)(B), it is the sum of --

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

> The number of days between the effective date of the initial IND, May 4, 1986, and the initial submission of the NDA, July 14, 1994, is a period of 2994 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

> The number of days between the initial submission of the NDA, July 14, 1994, to NDA approval, August 5, 1996, is a period of 754 days.

37 C.F.R. §1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on May 4, 1986, which were on or before April 7, 1981, the date the patent was issued, is a period of 0 days,

2994 days minus 0 days equals 2994 days,

and

the number of days in the period of the NDA, initial submission of July 14, 1994, which were on or before April 7, 1981, the date the patent was issued, is a period of 0 days,

754 days minus 0 days equals 754 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. §156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the applicant did not act with due diligence is 0 days,

therefore,

2994 days minus 0 days equals 2994 days.

754 days minus 0 days equals 754 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2994 days equals 1497 days.

Thus U.S. Patent No. 4,260,769 should be entitled to an extension of 2251 days (1497 days plus 754 days).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 2251 days to April 7, 1998, the original term of the patent (no terminal disclaimer was made), extends the term to June 5, 2004.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to August 5, 1996, the date of approval of the application, gives the date of August 5, 2010.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is June 5, 2004.

(5) If the original patent was issued after September 24, 1984,

This is not applicable for the patent.

(6) If the original patent was issued before September 24, 1984, and

(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--

(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

Adding 5 years to the original expiration date of the patent (April 7, 1998) gives the date of April 7, 2003.

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date; or

Comparing April 7, 2003, and June 5, 2004, April 7, 2003, is the earlier date and therefore the patent term should be extended to April 7, 2003.

(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--

This is not applicable for the patent.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Applicant is unaware of any additional information material to this Application for extension.

(14) Prescribed Fee:

The prescribed fee of $1,030.00 for receiving and acting on this application for extension of patent term is hereby authorized. Please charge Deposit Account No. 23-0455 in the amount of the fee above, or such greater or lesser amount of excess fees as the Commissioner determines is required by law.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Todd M. Crissey
Registration No. 37,807
Patent Department
WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, Michigan 48105
Telephone: (313) 996-7530
Facsimile: (313) 996-1553

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. §1.740.

DECLARATION

The undersigned is authorized to obligate WARNER-LAMBERT COMPANY, the licensee of U.S. Patent 4,260,769 and the agent of Merck & Company, the owner of record of the patent, to apply for an extension of term of this patent. I declare that: I have reviewed and understand the contents of this Application being submitted pursuant to 35 U.S.C. §156; that I believe that the patent is subject to extension pursuant to 37 C.F.R. §1.710; that I believe that the length of extension claimed is fully justified under 35 U.S.C. §156 and the applicable regulations; and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,260,769.

WARNER-LAMBERT COMPANY

Date: Sept. 27, 1996 By: Todd M. Crissey

Todd M. Crissey
Counsel, Patents
WARNER-LAMBERT COMPANY
Pharmaceutical Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
(313) 996-7530

TC1P4111.wp

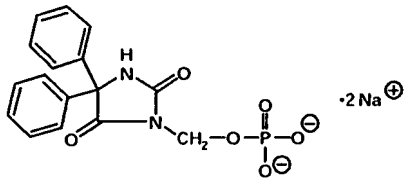
EXHIBIT 1
PACKAGE INSERT

Cerebyx®
(Fosphenytoin Sodium Injection)

DESCRIPTION

Cerebyx® (fosphenytoin sodium injection) is a prodrug intended for parenteral administration; its active metabolite is phenytoin. Each Cerebyx vial contains 75 mg/mL fosphenytoin sodium (hereafter referred to as fosphenytoin) equivalent to 50 mg/mL phenytoin sodium after administration. Cerebyx is supplied in vials as a ready-mixed solution in Water for Injection, USP, and Tromethamine, USP (TRIS), buffer adjusted to pH 8.6 to 9.0 with either Hydrochloric Acid, NF, or Sodium Hydroxide, NF. Cerebyx is a clear, colorless to pale yellow, sterile solution.

The chemical name of fosphenytoin is 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt. The molecular structure of fosphenytoin is:



The molecular weight of fosphenytoin is 406.24.

IMPORTANT NOTE: Throughout all Cerebyx® product labeling, the amount and concentration of fosphenytoin is expressed in terms of phenytoin sodium equivalents (PE). Fosphenytoin's weight is expressed as phenytoin sodium equivalents to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. Cerebyx should always be prescribed and dispensed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Introduction

Following parenteral administration of Cerebyx, fosphenytoin is converted to the anticonvulsant phenytoin. For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. The pharmacological and toxicological effects of fosphenytoin include those of phenytoin. However, the hydrolysis of fosphenytoin to phenytoin yields two metabolites, phosphate and formaldehyde. Formaldehyde is subsequently converted to formate, which is in turn metabolized via a folate dependent mechanism. Although phosphate and formaldehyde (formate) have potentially important biological effects, these effects typically occur at concentrations considerably in excess of those obtained when Cerebyx is administered under conditions of use recommended in this labeling.

Mechanism of Action

Fosphenytoin is a prodrug of phenytoin and accordingly, its anticonvulsant effects are attributable to phenytoin.

After IV administration to mice, fosphenytoin blocked the tonic phase of maximal electroshock seizures at doses equivalent to those effective for phenytoin. In addition to its ability to suppress maximal electroshock seizures in mice and rats, phenytoin exhibits anticonvulsant activity against kindled seizures in rats, audiogenic seizures in mice, and seizures produced by electrical stimulation of the brainstem in rats. The cellular mechanisms of phenytoin thought to be responsible for its anticonvulsant actions include modulation of voltage-dependent sodium channels of neurons, inhibition of calcium flux across neuronal membranes, modulation of voltage-dependent calcium channels of neurons, and enhancement of the sodium-potassium ATPase activity of neurons and glial cells. The modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin.

Pharmacokinetics and Drug Metabolism

Fosphenytoin

Absorption/Bioavailability: *Intravenous:* When Cerebyx is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin has a half-life of approximately 15 minutes.

Intramuscular. Fosphenytoin is completely bioavailable following IM administration of Cerebyx. Peak concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution: Fosphenytoin is extensively bound (95% to 99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution of fosphenytoin increases with Cerebyx dose and rate, and ranges from 4.3 to 10.8 liters.

Metabolism and Elimination: The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. The mechanism of fosphenytoin conversion has not been determined, but phosphatases probably play a major role. Fosphenytoin is not excreted in urine. Each mmol of fosphenytoin is metabolized to 1 mmol of phenytoin, phosphate, and formate (see CLINICAL PHARMACOLOGY, Introduction and PRECAUTIONS, Phosphate Load for Renally Impaired Patients).

Phenytoin (after Cerebyx administration)

In general, IM administration of Cerebyx generates systemic phenytoin concentrations that are similar enough to oral phenytoin sodium to allow essentially interchangeable use.

The pharmacokinetics of fosphenytoin following IV administration of Cerebyx, however, are complex, and when used in an emergency setting (eg, status epilepticus), differences in rate of availability of phenytoin could be critical. Studies have therefore empirically determined an infusion rate for Cerebyx that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion.

A dose of 15 to 20 mg PE/kg of Cerebyx infused at 100 to 150 mg PE/min yields plasma free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (eg, parenteral Dilantin®) is administered at 50 mg/min (see DOSAGE AND ADMINISTRATION, WARNINGS).

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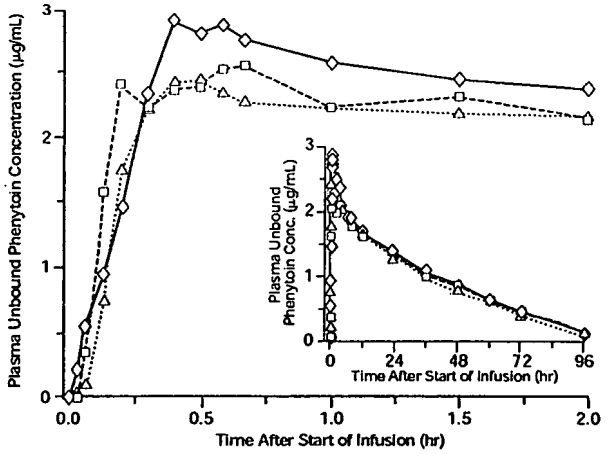

FIGURE 1. Mean plasma unbound phenytoin concentrations following IV administration of 1200 mg PE Cerebyx infused at 100 mg PE/min (triangles) or 150 mg PE/min (squares) and 1200 mg Dilantin infused at 50 mg/min (diamonds) to healthy subjects (N = 12). Inset shows time course for the entire 96-hour sampling period.

Following administration of single IV Cerebyx doses of 400 to 1200 mg PE, mean maximum total phenytoin concentrations increase in proportion to dose, but do not change appreciably with changes in infusion rate. In contrast, mean maximum unbound phenytoin concentrations increase with both dose and rate.

Absorption/Bioavailability: Fosphenytoin is completely converted to phenytoin following IV administration, with a half-life of approximately 15 minutes. Fosphenytoin is also completely converted to phenytoin following IM administration and plasma total phenytoin concentrations peak in approximately 3 hours.

Distribution: Phenytoin is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. In the absence of fosphenytoin, approximately 12% of total plasma phenytoin is unbound over the clinically relevant concentration range. However, fosphenytoin displaces phenytoin from plasma protein binding sites. This increases the fraction of phenytoin unbound (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin (approximately 0.5 to 1 hour postinfusion).

Metabolism and Elimination: Phenytoin derived from administration of Cerebyx is extensively metabolized in the liver and excreted in urine primarily as 5-(p-hydroxyphenyl)-5-phenylhydantoin and its glucuronide; little unchanged phenytoin (1%-5% of the Cerebyx dose) is recovered in urine. Phenytoin hepatic metabolism is saturable, and following administration of single IV Cerebyx doses of 400 to 1200 mg PE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0 to 28.9 hr) following Cerebyx administration at these doses are similar to those after equal doses of parenteral Dilantin and tend to be greater at higher plasma phenytoin concentrations.

Special Populations

Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentrations may be more useful in these patient populations. After IV administration of Cerebyx to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

Age: The effect of age was evaluated in patients 5 to 98 years of age. Patient age had no significant impact on fosphenytoin pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

Gender and Race: Gender and race have no significant impact on fosphenytoin or phenytoin pharmacokinetics.

Pediatrics: Only limited pharmacokinetic data are available in children (N=8; age 5 to 10 years). In these patients with status epilepticus who received loading doses of Cerebyx, the plasma fosphenytoin, total phenytoin, and unbound phenytoin concentration-time profiles did not signal any major differences from those in adult patients with status epilepticus receiving comparable doses.

Clinical Studies

Infusion tolerance was evaluated in clinical studies. One double-blind study assessed infusion-site tolerance of equivalent loading doses (15-20 mg PE/kg) of Cerebyx infused at 150 mg PE/min or phenytoin infused at 50 mg/min. The study demonstrated better local tolerance (pain and burning at the infusion site), fewer disruptions of the infusion, and a shorter infusion period for Cerebyx-treated patients (Table 1).

TABLE 1. Infusion Tolerance of Equivalent Loading Doses of IV Cerebyx and IV Phenytoin

	IV Cerebyx N=90	IV Phenytoin N=22
Local Intolerance	9%[a]	90%
Infusion Disrupted	21%	67%
Average Infusion Time	13 min	44 min

[a]Percent of patients.

Cerebyx-treated patients, however, experienced more systemic sensory disturbances (see PRECAUTIONS, Sensory Disturbances).

Infusion disruptions in Cerebyx-treated patients were primarily due to systemic burning, pruritus, and/or paresthesia while those in phenytoin-treated patients were primarily due to pain and burning at the infusion site (see Table 1).

In a double-blind study investigating temporary substitution of Cerebyx for oral phenytoin, IM Cerebyx was as well-tolerated as IM placebo. IM Cerebyx resulted in a slight increase in transient, mild to moderate local itching (23% of patients vs 11% of IM placebo-treated patients at any time during the study). This study also demonstrated that equimolar doses of IM Cerebyx may be substituted for oral phenytoin sodium with no dosage adjustments needed when initiating IM or

returning to oral therapy. In contrast, switching between IM and oral phenytoin requires dosage adjustments because of slow and erratic phenytoin absorption from muscle.

INDICATIONS AND USAGE

Cerebyx is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of Cerebyx in this use has not been systematically evaluated for more than 5 days.

Cerebyx can be used for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin.

CONTRAINDICATIONS

Cerebyx is contraindicated in patients who have demonstrated hypersensitivity to Cerebyx or its ingredients, or to phenytoin or other hydantoins.

Because of the effect of parenteral phenytoin on ventricular automaticity, Cerebyx is contraindicated in patients with sinus bradycardia, sino-atrial block, second and third degree A-V block, and Adams-Stokes syndrome.

WARNINGS

DOSES OF CEREBYX ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS IN THIS LABELING (PE=phenytoin sodium equivalent).

DO NOT, THEREFORE, MAKE ANY ADJUSTMENT IN THE RECOMMENDED DOSES WHEN SUBSTITUTING CEREBYX FOR PHENYTOIN SODIUM OR VICE VERSA.

The following warnings are based on experience with Cerebyx or phenytoin.

Status Epilepticus Dosing Regimen

• Do not administer Cerebyx at a rate greater than 150 mg PE/min.

The dose of IV Cerebyx (15 to 20 mg PE/kg) that is used to treat status epilepticus is administered at a maximum rate of 150 mg PE/min. The typical Cerebyx infusion administered to a 50 kg patient would take between 5 and 7 minutes. Note that the delivery of an identical molar dose of phenytoin using parenteral Dilantin or generic phenytoin sodium injection cannot be accomplished in less than 15 to 20 minutes because of the untoward cardiovascular effects that accompany the direct intravenous administration of phenytoin at rates greater than 50 mg/min.

If rapid phenytoin loading is a primary goal, IV administration of Cerebyx is preferred because the time to achieve therapeutic plasma phenytoin concentrations is greater following IM than that following IV administration (see DOSAGE AND ADMINISTRATION).

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

Cardiovascular Depression

Hypotension may occur, especially after IV administration at high doses and high rates of administration. Following administration of phenytoin, severe cardiovascular reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients. Therefore, careful cardiac monitoring is needed when administering IV loading doses of Cerebyx. Reduction in rate of administration or discontinuation of dosing may be needed.

Cerebyx should be used with caution in patients with hypotension and severe myocardial insufficiency.

Rash

Cerebyx should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous, or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further Cerebyx or phenytoin administration is contraindicated.

Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, Cerebyx should be immediately discontinued and not readministered.

Hemopoietic System

Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports that have suggested a relationship between phenytoin and the development of lymphadenopathy (local or generalized), including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash, and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Alcohol Use

Acute alcohol intake may increase plasma phenytoin concentrations while chronic alcohol use may decrease plasma concentrations.

Usage in Pregnancy

Clinical:

A. Risks to Mother. An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

B. Risks to the Fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or two-to three-fold that in the general population. However, the relative contributions of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

C. Postpartum Period. A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Preclinical: Increased frequencies of malformations (brain, cardiovascular, digit, and skeletal anomalies), death, growth retardation, and functional impairment (chromodacryorrhea, hyperactivity, circling) were observed among the offspring of rats receiving fosphenytoin during pregnancy. Most of the adverse effects on embryo-fetal development occurred at doses of 33 mg PE/kg or higher (approximately 30% of the maximum human loading dose or higher on a mg/m² basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 μg/mL or greater. Maternal toxicity was often associated with these doses and plasma concentrations, however, there is no evidence to suggest that the developmental effects were secondary to the maternal effects. The single occurrence of a rare brain malformation at a non-maternotoxic dose of 17 mg PE/kg (approximately 10% of the maximum human loading dose on a mg/m² basis) was also considered drug-induced. The developmental effects of fosphenytoin in rats were similar to those which have been reported following administration of phenytoin to pregnant rats.

No effects on embryo-fetal development were observed when rabbits were given up to 33 mg PE/kg of fosphenytoin (approximately 50% of the maximum human loading dose on a mg/m² basis) during pregnancy. Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m² basis) to pregnant rabbits.

PRECAUTIONS

General: (Cerebyx specific)

Sensory Disturbances

Severe burning, itching, and/or paresthesia were reported by 7 of 16 normal volunteers administered IV Cerebyx at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min). The severe sensory disturbance lasted from 3 to 50 minutes in 6 of these subjects and for 14 hours in the seventh subject. In some cases, milder sensory disturbances persisted for as long as 24 hours. The location of the discomfort varied among subjects with the groin mentioned most frequently as an area of discomfort. In a separate cohort of 16 normal volunteers (taken from 2 other studies) who were administered IV Cerebyx at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min), none experienced severe disturbances, but most experienced mild to moderate itching or tingling.

Patients administered Cerebyx at doses of 20 mg PE/kg at 150 mg PE/min are expected to experience discomfort of some degree. The occurrence and intensity of the discomfort can be lessened by slowing or temporarily stopping the infusion.

The effect of continuing infusion unaltered in the presence of these sensations is unknown. No permanent sequelae have been reported thus far. The pharmacologic basis for these positive sensory phenomena is unknown, but other phosphate ester drugs, which deliver smaller phosphate loads, have been associated with burning, itching, and/or tingling predominantly in the groin area.

Phosphate Load

The phosphate load provided by Cerebyx (0.0037 mmol phosphate/mg PE Cerebyx) should be considered when treating patients who require phosphate restriction, such as those with severe renal impairment.

IV Loading in Renal and/or Hepatic Disease or in Those With Hypoalbuminemia

After IV administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see CLINICAL PHARMACOLOGY: Special Populations, and DOSAGE AND ADMINISTRATION: Dosing in Special Populations).

General: (phenytoin associated)

Cerebyx is *not* indicated for the treatment of *absence seizures*.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. *Slow metabolism* may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.

Phenytoin has been infrequently associated with the exacerbation of *porphyria*. Caution should be exercised when Cerebyx is used in patients with this disease.

Hyperglycemia, resulting from phenytoin's inhibitory effect on insulin release, has been reported. Phenytoin may also raise the serum glucose concentrations in diabetic patients. Plasma concentrations of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely, irreversible cerebellar dysfunction. Accordingly, at the first sign of *acute toxicity*, determination of plasma phenytoin concentrations is recommended (see PRECAUTIONS: Laboratory Tests). Cerebyx dose reduction is indicated if phenytoin concentrations are excessive; if symptoms persist, administration of Cerebyx should be discontinued.

The liver is the primary site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

Phenytoin and other hydantoins are not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin has the potential to lower serum folate levels.

Laboratory Tests

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10 to 20 μg/mL, (unbound phenytoin concentrations of 1 to 2 μg/mL). Following Cerebyx administration, it is recommended that phenytoin concentrations not be monitored until conversion to phenytoin is essentially complete. This occurs within approximately 2 hours after the end of IV infusion and 4 hours after IM injection.

Prior to complete conversion, commonly used immunoanalytical techniques, such as TDx®/TDxFLx™ (fluorescence polarization) and Emit® 2000 (enzyme multiplied), may significantly overestimate plasma phenytoin concentrations because of cross-reactivity with fosphenytoin. The error is dependent on plasma phenytoin and fosphenytoin concentration (influenced by Cerebyx dose, route and rate of administration, and time of sampling relative to dosing), and analytical method. Chromatographic assay methods accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Prior to complete conversion, blood samples for

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phenytoin monitoring should be collected in tubes containing EDTA as an anticoagulant to minimize *ex vivo* conversion of fosphenytoin to phenytoin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not reflect phenytoin concentrations ultimately achieved.

Drug Interactions

No drugs are known to interfere with the conversion of fosphenytoin to phenytoin. Conversion could be affected by alterations in the level of phosphatase activity, but given the abundance and wide distribution of phosphatases in the body it is unlikely that drugs would affect this activity enough to affect conversion of fosphenytoin to phenytoin. Drugs highly bound to albumin could increase the unbound fraction of fosphenytoin. Although, it is unknown whether this could result in clinically significant effects, caution is advised when administering Cerebyx with other drugs that significantly bind to serum albumin.

The pharmacokinetics and protein binding of fosphenytoin, phenytoin, and diazepam were not altered when diazepam and Cerebyx were concurrently administered in single submaximal doses.

The most significant drug interactions following administration of Cerebyx are expected to occur with drugs that interact with phenytoin. Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

The most commonly occurring drug interactions are listed below:

- Drugs that may increase plasma phenytoin concentrations include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.
- Drugs that may decrease plasma phenytoin concentrations include: carbamazepine, chronic alcohol abuse, reserpine.
- Drugs that may either increase or decrease plasma phenytoin concentrations include: phenobarbital, valproic acid, and sodium valproate. Similarly, the effects of phenytoin on phenobarbital, valproic acid and sodium plasma valproate concentrations are unpredictable.
- Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and Cerebyx dosage may need to be adjusted.
- Drugs whose efficacy is impaired by phenytoin include: anticoagulants, corticosteroids, coumarin, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, rifampin, quinidine, theophylline, vitamin D.

Monitoring of plasma phenytoin concentrations may be helpful when possible drug interactions are suspected (see Laboratory Tests).

Drug/Laboratory Test Interactions

Phenytoin may decrease serum concentrations of T_4. It may also produce artifactually low results in dexamethasone or metyrapone tests. Phenytoin may also cause increased serum concentrations of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations following Cerebyx administration (see Laboratory Tests).

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of fosphenytoin has not been studied. Assessment of the carcinogenic potential of phenytoin in mice and rats is ongoing.

Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin in the presence of metabolic activation. No evidence of mutagenicity was observed in bacteria (Ames test) or Chinese hamster lung cells *in vitro*, and no evidence for clastogenic activity was observed in an *in vivo* mouse bone marrow micronucleus test.

No effects on fertility were noted in rats of either sex given fosphenytoin. Maternal toxicity and altered estrous cycles, delayed mating, prolonged gestation length, and developmental toxicity were observed following administration of fosphenytoin during mating, gestation, and lactation at doses of 50 mg PE/kg or higher (approximately 40% of the maximum human loading dose or higher on a mg/m² basis).

Pregnancy - Category D: (see WARNINGS)

Use in Nursing Mothers

It is not known whether fosphenytoin is excreted in human milk.

Following administration of Dilantin, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving Cerebyx.

Pediatric Use

The safety of Cerebyx in pediatric patients has not been established.

Geriatric Use

No systematic studies in geriatric patients have been conducted. Phenytoin clearance tends to decrease with increasing age (see CLINICAL PHARMACOLOGY: Special Populations).

ADVERSE REACTIONS

The more important adverse clinical events caused by the IV use of Cerebyx or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route. The rate of administration is very important; for Cerebyx, it should not exceed 150 mg PE/min.

The adverse clinical events most commonly observed with the use of Cerebyx in clinical trials were nystagmus, dizziness, pruritus, paresthesia, headache, somnolence, and ataxia. With two exceptions, these events are commonly associated with the administration of IV phenytoin. Paresthesia and pruritus, however, were seen much more often following Cerebyx administration and occurred more often with IV Cerebyx administration than with IM Cerebyx administration. These events were dose and rate related; most alert patients (41 of 64; 64%) administered doses of ≥15 mg PE/kg at 150 mg PE/min experienced discomfort of some degree. These sensations, generally described as itching, burning, or tingling, were usually not at the infusion site. The location of the discomfort varied with the groin mentioned most frequently as a site of involvement. The paresthesia and pruritus were transient events that occurred within several minutes of the start of infusion and generally resolved within 10 minutes after completion of Cerebyx infusion. Some patients experienced symptoms for hours. These events did not increase in severity with repeated administration. Concurrent adverse events or clinical laboratory change suggesting an allergic process were not seen (see PRECAUTIONS, Sensory Disturbances).

Approximately 2% of the 859 individuals who received Cerebyx in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were pruritus (0.5%), hypotension (0.3%), and bradycardia (0.2%).

Dose and Rate Dependency of Adverse Events Following IV Cerebyx: The incidence of adverse events tended to increase as both dose and infusion rate increased. In particular, at doses of ≥15 mg PE/kg and rates ≥150 mg PE/min, transient pruritus, tinnitus, nystagmus, somnolence, and ataxia occurred 2 to 3 times more often than at lower doses or rates.

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Incidence in Controlled Clinical Trials

All adverse events were recorded during the trials by the clinical investigators using terminolog their own choosing. Similar types of events were grouped into standardized categories using m fied COSTART dictionary terminology. These categories are used in the tables and listings belo with the frequencies representing the proportion of individuals exposed to Cerebyx or compara therapy.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other f tors may differ from those prevailing during clinical studies. Similarly, the cited frequencies ca be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide th prescribing physician with one basis to estimate the relative contribution of drug and nondrug tors to the adverse event incidences in the population studied.

Incidence in Controlled Clinical Trials - IV Administration To Patients With Epilepsy or Neurosurgical Patients: Table 2 lists treatment-emergent adverse events that occurred in at lea 2% of patients treated with IV Cerebyx at the maximum dose and rate in a randomized, double-blind, controlled clinical trial where the rates for phenytoin and Cerebyx administration would h resulted in equivalent systemic exposure to phenytoin.

TABLE 2. Treatment-Emergent Adverse Event Incidence Following IV Administration at the Maximum Dose and Rate to Patients With Epilepsy or Neurosurgical Patients (Events in at Least 2% of Cerebyx-Treated Patients)

BODY SYSTEM Adverse Event	IV Cerebyx N = 90	IV Phenytoin N = 22
BODY AS A WHOLE		
Pelvic Pain	4.4	0.0
Asthenia	2.2	0.0
Back Pain	2.2	0.0
Headache	2.2	4.5
CARDIOVASCULAR		
Hypotension	7.7	9.1
Vasodilatation	5.6	4.5
Tachycardia	2.2	0.0
DIGESTIVE		
Nausea	8.9	13.6
Tongue Disorder	4.4	0.0
Dry Mouth	4.4	4.5
Vomiting	2.2	9.1
NERVOUS		
Nystagmus	44.4	59.1
Dizziness	31.1	27.3
Somnolence	20.0	27.3
Ataxia	11.1	18.2
Stupor	7.7	4.5
Incoordination	4.4	4.5
Paresthesia	4.4	0.0
Extrapyramidal Syndrome	4.4	0.0
Tremor	3.3	9.1
Agitation	3.3	0.0
Hypesthesia	2.2	9.1
Dysarthria	2.2	0.0
Vertigo	2.2	0.0
Brain Edema	2.2	4.5
SKIN AND APPENDAGES		
Pruritus	48.9	4.5
SPECIAL SENSES		
Tinnitus	8.9	9.1
Diplopia	3.3	0.0
Taste Perversion	3.3	0.0
Amblyopia	2.2	9.1
Deafness	2.2	0.0

Incidence in Controlled Trials - IM Administration to Patients With Epilepsy. Table 3 lists treatm emergent adverse events that occurred in at least 2% of Cerebyx-treated patients in a double-b randomized, controlled clinical trial of adult epilepsy patients receiving either IM Cerebyx subst ed for oral Dilantin or continuing oral Dilantin. Both treatments were administered for 5 days.

TABLE 3. Treatment-Emergent Adverse Event Incidence Following Substitution of IM Cerebyx for Oral Dilantin in Patients With Epilepsy (Events in at Least 2% of Cerebyx-Treated Patients)

BODY SYSTEM Adverse Event	IM Cerebyx N = 179	Oral Dilantin N = 61
BODY AS A WHOLE		
Headache	8.9	4.9
Asthenia	3.9	3.3
Accidental Injury	3.4	6.6
DIGESTIVE		
Nausea	4.5	0.0
Vomiting	2.8	0.0
HEMATOLOGIC AND LYMPHATIC		
Ecchymosis	7.3	4.9
NERVOUS		
Nystagmus	15.1	8.2
Tremor	9.5	13.1
Ataxia	8.4	8.2
Incoordination	7.8	4.9
Somnolence	6.7	9.8
Dizziness	5.0	3.3
Paresthesia	3.9	3.3
Reflexes Decreased	2.8	4.9
SKIN AND APPENDAGES		
Pruritus	2.8	0.0

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Adverse Events During All Clinical Trials

Cerebyx has been administered to 859 individuals during all clinical trials. All adverse events seen at least twice are listed in the following, except those already included in previous tables and listings. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 individuals; infrequent adverse events are those occurring in 1/100 to 1/1000 individuals.

Body As a Whole: *Frequent:* fever, injection-site reaction, infection, chills, face edema, injection-site pain; *Infrequent:* sepsis, injection-site inflammation, injection-site edema, injection-site hemorrhage, flu syndrome, malaise, generalized edema, shock, photosensitivity reaction, cachexia, cryptococcosis.

Cardiovascular: *Frequent:* hypertension; *Infrequent:* cardiac arrest, migraine, syncope, cerebral hemorrhage, palpitation, sinus bradycardia, atrial flutter, bundle branch block, cardiomegaly, cerebral infarct, postural hypotension, pulmonary embolus, QT interval prolongation, thrombophlebitis, ventricular extrasystoles, congestive heart failure.

Digestive: *Frequent:* constipation; *Infrequent:* dyspepsia, diarrhea, anorexia, gastrointestinal hemorrhage, increased salivation, liver function tests abnormal, tenesmus, tongue edema, dysphagia, flatulence, gastritis, ileus.

Endocrine: *Infrequent:* diabetes insipidus.

Hematologic and Lymphatic: *Infrequent:* thrombocytopenia, anemia, leukocytosis, cyanosis, hypochromic anemia, leukopenia, lymphadenopathy, petechia.

Metabolic and Nutritional: *Frequent:* hypokalemia; *Infrequent:* hyperglycemia, hypophosphatemia, alkalosis, acidosis, dehydration, hyperkalemia, ketosis.

Musculoskeletal: *Frequent:* myasthenia; *Infrequent:* myopathy, leg cramps, arthralgia, myalgia.

Nervous: *Frequent:* reflexes increased, speech disorder, dysarthria, intracranial hypertension, thinking abnormal, nervousness, hypesthesia; *Infrequent:* confusion, twitching, Babinski sign positive, circumoral paresthesia, hemiplegia, hypotonia, convulsion, extrapyramidal syndrome, insomnia, meningitis, depersonalization, CNS depression, depression, hypokinesia, hyperkinesia, brain edema, paralysis, psychosis, aphasia, emotional lability, coma, hyperesthesia, myoclonus, personality disorder, acute brain syndrome, encephalitis, subdural hematoma, encephalopathy, hostility, akathisia, amnesia, neurosis.

Respiratory: *Frequent:* pneumonia; *Infrequent:* pharyngitis, sinusitis, hyperventilation, rhinitis, apnea, aspiration pneumonia, asthma, dyspnea, atelectasis, cough increased, sputum increased, epistaxis, hypoxia, pneumothorax, hemoptysis, bronchitis.

Skin and Appendages: *Frequent:* rash; *Infrequent:* maculopapular rash, urticaria, sweating, skin discoloration, contact dermatitis, pustular rash, skin nodule.

Special Senses: *Frequent:* taste perversion; *Infrequent:* deafness, visual field defect, eye pain, conjunctivitis, photophobia, hyperacusis, mydriasis, parosmia, ear pain, taste loss.

Urogenital: *Infrequent:* urinary retention, oliguria, dysuria, vaginitis, albuminuria, genital edema, kidney failure, polyuria, urethral pain, urinary incontinence, vaginal moniliasis.

OVERDOSAGE

There is no experience with Cerebyx overdosage in humans. The median lethal dose of fosphenytoin given intravenously in mice and rats was 156 mg PE/kg and approximately 250 mg PE/kg, or about 0.6 and 2 times, respectively, the maximum human loading dose on a mg/m² basis. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, and hypoactivity.

Because Cerebyx is a prodrug of phenytoin, the following information may be helpful. Initial symptoms of acute phenytoin toxicity are nystagmus, ataxia, and dysarthria. Other signs include tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting, coma, and hypotension. Depression of respiratory and circulatory systems leads to death. There are marked variations among individuals with respect to plasma phenytoin concentrations where toxicity occurs. Lateral gaze nystagmus usually appears at 20 μg/mL, ataxia at 30 μg/mL, and dysarthria and lethargy appear when the plasma concentration is over 40 μg/mL. However, phenytoin concentrations as high as 50 μg/mL have been reported without evidence of toxicity. As much as 25 times the therapeutic phenytoin dose has been taken, resulting in plasma phenytoin concentrations over 100 μg/mL, with complete recovery.

Treatment is nonspecific since there is no known antidote to Cerebyx or phenytoin overdosage. The adequacy of the respiratory and circulatory systems should be carefully observed, and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children. In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Formate and phosphate are metabolites of fosphenytoin and therefore may contribute to signs of toxicity following overdosage. Signs of formate toxicity are similar to those of methanol toxicity and are associated with severe anion-gap metabolic acidosis. Large amounts of phosphate, delivered rapidly, could potentially cause hypocalcemia with paresthesia, muscle spasms, and seizures. Ionized free calcium levels can be measured and, if low, used to guide treatment.

DOSAGE AND ADMINISTRATION

The dose, concentration in dosing solutions, and infusion rate of IV Cerebyx is expressed as phenytoin sodium equivalents (PE) to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. Cerebyx should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). Cerebyx has important differences in administration from those for parenteral phenytoin sodium (see below).

Products with particulate matter or discoloration should not be used. Prior to IV infusion, dilute Cerebyx in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/mL.

Status Epilepticus

The loading dose of Cerebyx is 15 to 20 mg PE/kg administered at 100 to 150 mg PE/min.

Because of the risk of hypotension, fosphenytoin should be administered no faster than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10 to 20 minutes after the end of Cerebyx infusions.

Because the full antiepileptic effect of phenytoin, whether given as Cerebyx or parenteral phenytoin, is not immediate, other measures, including concomitant administration of an IV benzodiazepine, will usually be necessary for the control of status epilepticus.

The loading dose should be followed by maintenance doses of Cerebyx, or phenytoin either orally or parenterally.

If administration of Cerebyx does not terminate seizures, the use of other anticonvulsants and other appropriate measures should be considered.

IM Cerebyx should not be used in the treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration. If IV access is impossible, loading doses of Cerebyx have been given by the IM route for other indications.

Cerebyx®
(Fosphenytoin Sodium Injection)

Nonemergent Loading and Maintenance Dosing

The loading dose of Cerebyx is 10 - 20 mg PE/kg given IV or IM. The rate of administration for IV Cerebyx should be no greater than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10 to 20 minutes after the end of Cerebyx infusions.

The initial daily maintenance dose of Cerebyx is 4 - 6 mg PE/kg/day.

IM or IV Substitution For Oral Phenytoin Therapy

Cerebyx can be substituted for oral phenytoin sodium therapy at the same total daily dose.

Dilantin capsules are approximately 90% bioavailable by the oral route. Phenytoin, supplied as Cerebyx, is 100% bioavailable by both the IM and IV routes. For this reason, plasma phenytoin concentrations may increase modestly when IM or IV Cerebyx is substituted for oral phenytoin sodium therapy.

The rate of administration for IV Cerebyx should be no greater than 150 mg PE/min.

In controlled trials, IM Cerebyx was administered as a single daily dose utilizing either 1 or 2 injection sites. Some patients may require more frequent dosing.

Dosing In Special Populations

Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see CLINICAL PHARMACOLOGY: Special Populations). Unbound phenytoin concentrations may be more useful in these patient populations. After IV Cerebyx administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

Elderly Patients: Age does not have a significant impact on the pharmacokinetics of fosphenytoin following Cerebyx administration. Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

Pediatric: The safety of Cerebyx in pediatric patients has not been established.

HOW SUPPLIED

Cerebyx injection is supplied as follows:

10 mL per vial — Each vial contains fosphenytoin sodium 750 mg equivalent to 500 mg of phenytoin sodium:

N 0071-4008-10. Packages of 10.

2 mL per vial — Each vial contains fosphenytoin sodium 150 mg equivalent to 100 mg of phenytoin sodium:

N 0071-4007-05. Packages of 25.

Both sizes of vials contain Tromethamine, USP (TRIS), Hydrochloric Acid, NF, or Sodium Hydroxide, NF, and Water for Injection, USP.

Cerebyx should always be prescribed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION).

Storage

Store under refrigeration at 2°C to 8°C (36°F to 46°F). The product should not be stored at room temperature for more than 48 hours. Vials that develop particulate matter should not be used.

Caution: Federal law prohibits dispensing without prescription.

Issued date: July 1996

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

EXHIBIT 2
APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-450

AUG - 5 1996

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Ms. Janeth L. Turner
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Turner:

Please refer to your July 14, 1994 new drug application and your resubmission dated February 22, 1995 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cerebyx® (fosphenytoin sodium) Injection 75 mg/mL (50 mg/mL PE).

We also acknowledge receipt of your additional correspondence and amendments dated:

February 27, 1996	April 12, 1996	May 8, 1996
March 13, 1996	May 1, 1996	July 12, 1996
March 14, 1996	May 2, 1996 (2)	July 30, 1996

This new drug application provides for the following:

Cerebyx® is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of Cerebyx® in this use has not been systematically evaluated for more than 5 days.

Cerebyx® can be used for the control of generalized convulsive status epilepticus and prevention and prevention and treatment of seizures occurring during neurosurgery. It can also be substituted, short-term, for oral phenytoin.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated July 12, 1996 with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows:

1. Please correct the legend to Figure 1 to read "...1200 mg PE Cerebyx infused..." rather than "...1200 mg Cerebyx infused...."

2. WARNINGS: Usage in Pregnancy: *Clinical:* section

B. *Risks to the Fetus.*

Paragraph 1, last sentence: please change "contribution" to "contributions".

3. WARNINGS: Usage in Pregnancy: *preclinical:* section

The wording of dose comparisons and plasma level data should be made consistent as follows:

Para 1, sentence 2: ... (approximately 30% of the maximum human loading dose or higher on a mg/m^2 basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 μg/mL or greater.

Para 1, sentence 4: ... (approximately 10% of the maximum human loading dose on a mg/m^2 basis) ....

Para 2, sentence 1: ... (approximately 50% ....

Para 2, sentence 2: ... (approximately 120% ....

4. PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility; section

Para 3, last sentence: ... at doses of 50 mg PE/kg or higher (approximately 40 % of the maximum human loading dose or higher on a mg/m^2 basis).

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-450. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Phase IV Commitment

We remind you of your Phase 4 commitment specified in your submission dated April 12, 1996 and amended on July 12, & 30, 1996. This commitment is listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment." Your commitment is as follows:

> "As a Phase IV commitment, we agree to conduct a pharmacokinetic and safety study in appropriate pediatric populations to support the safe use of Cerebyx, and to update the package insert with this information. We will discuss with the Agency the appropriate pediatric populations and pharmacokinetic and safety evaluations necessary to meet this commitment. While Parke-Davis is very interested in completing this commitment as expeditiously as possible, a time frame for completion is dependent on these discussions."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact: Robbin Nighswander, R.Ph.
Regulatory Management Officer
(301) 594-2777

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

EXHIBIT 3
PATENT

United States Patent [19]

Stella et al.

[11] **4,260,769**

[45] **Apr. 7, 1981**

[54] **5,5-DIPHENYLHYDANTOINS**

[75] Inventors: **Valentino J. Stella, Lawrence; Kenneth B. Sloan, Eudora, both of Kans.**

[73] Assignee: **INTERx Research Corporation, Lawrence, Kans.**

[21] Appl. No.: **33,234**

[22] Filed: **Apr. 25, 1979**

Related U.S. Application Data

[62] Division of Ser. No. 790,087, Apr. 22, 1977, Pat. No. 4,163,058.

[51] **Int. Cl.**[3] **C07F 9/06**

[52] **U.S. Cl.** **548/112**

[58] **Field of Search** 548/312, 112

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,928,841	3/1960	McConnell et al.	548/312
3,676,454	7/1972	Vida	548/312
3,741,978	6/1973	Jamison	548/112
3,835,151	9/1974	Havera et al.	548/312
3,920,686	11/1975	Samour	548/312
3,946,034	3/1976	Porret et al.	548/312
4,163,058	7/1979	Stella et al.	548/312

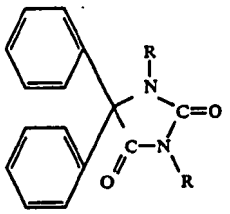
FOREIGN PATENT DOCUMENTS

2064474	7/1971	Fed. Rep. of Germany	548/312
1093728	5/1955	France	548/312

Primary Examiner—John D. Randolph
Assistant Examiner—Jane T. Fan
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

Novel 5,5-diphenylhydantoins useful as anticonvulsants, antiepileptics and antiarrhythmics have the structural formula:



wherein each R is hydrogen or $-CH(R_1)-X-P(O)-(OH)_2$, R_1 is hydrogen or C_1–C_7 straight or branched chain alkyl, and X is O or S, with the proviso that both R's cannot simultaneously be hydrogen.

3 Claims, No Drawings

5,5-DIPHENYLHYDANTOINS

This is a division of application Ser. No. 790,087, filed Apr. 22, 1977, now U.S. Pat. No. 4,163,058.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel and therapeutically useful derivatives of phenytoin. More particularly, the present invention concerns the discovery of a group of novel derivatives of phenytoin which offer enhanced solubility over phenytoin per se.

These compounds are extremely useful as anticonvulsants, antiepileptics and antiarrhythmics and can be administered to warm-blooded animals (e.g., humans) per se or in pharmaceutical composition form when admixed with a suitable nontoxic pharmaceutically acceptable carrier.

2. Description of the Prior Art

A pharmaceutical and medical need exists for new and useful compounds indicated from the management of epilepsy and other types of convulsive states, and cardiac arrythmics. The need exists because compounds such as 5,5-diphenylhydantoin, generally referred to as diphenylhydantoin or phenytoin, which is most commonly and widely used for the treatment of these conditions possess extremely low solubility and hence, low bioavailability per se as well as from pharmaceutical dosage forms. For example, 5,5-diphenylhydantoin which has a therapeutic index between 1 and 2, a pKa of 8.3, and a solubility of less than 2 mg. in 100 ml at 37° C. often produces unpredictable and erractic release patterns, both in vitro and in vivo. Also, when 5,5-diphenylhydantoin is orally administered in the form of its sodium salt, it frequently causes gastric irritation due to the alkalinity of the administered dosage form. For intravenous administration, sodium 5,5-diphenylhydantoin is generally used in a formulation comprising 40% propylene glycol and 10% alcohol in water, adjusted with sodium hydroxide to a high alkaline pH. Intravenous administration of this formulation frequently leads to precipitation of 5,5-diphenylhydantoin as well as erractic blood levels. Intramuscular use of sodium 5,5-diphenylhydantoin has been shown to precipitate 5,5-diphenylhydantoin at the injection site leading to delayed and erractic 5,5-diphenylhydantoin release. Other hydantoins have similar problems to those seen with 5,5-diphenylhydantoin. This common and wide use of the hydantoins with their accompanying disadvantages, and specifically, their low solubilities, creates an immediate and pressing need for new and useful pharmaceutical compounds that possess therapeutic properties useful for treating epilepsy and other convulsive states, and cardiac arrythmics, while remaining essentially free from the unwanted effects associated with the prior art compounds.

U.S. Pat. No. 3,595,862 claims the potential usefulness of N,N'-bis(acyloxymethyl)5,5-diphenylhydantoin compounds as effective anticonvulsants. The compounds of this patent include those in which the acyloxy groups are acetoxy, acryloxy, methacryloyloxy, propionoxy and benzoyloxy. The compounds are inferior in solubility to the compounds claimed in this application and in fact have solubility characteristics similar to 5,5-diphenylhydantoin itself.

SUMMARY OF THE INVENTION

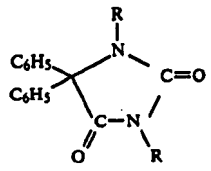
Accordingly, it is an immediate object of this invention to provide novel pharmaceutical compounds that are useful as antiepileptics, anticonvulsants and antiarrythmics.

Another object of this invention is to provide novel and useful derivatives of diphenylhydantoin which are characterized as being substantially more soluble than the parent specie per se.

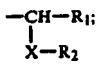
Still, another object of this invention is to provide novel and useful derivatives of diphenylhydantoin which, in addition to exhibiting enhanced solubility, are essentially free from the unwanted effects associated with the physical and chemical properties of prior art derivatives.

Finally, another object of the present invention is to provide new and useful derivatives of diphenylhydantoin as characterized above which further exhibit enhanced stability such that they can be tolerated in conventional pharmaceutical dosage formulations.

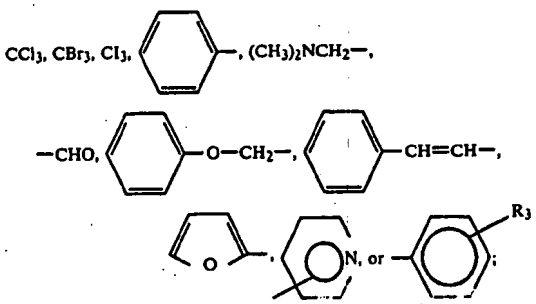
All the foregoing objects are achieved by administering to a warm-blooded animal in need of anticonvulsants and/or antiepileptic therapy, a compound having the formula:



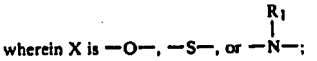
wherein R represents H or a member selected from the group consisting of



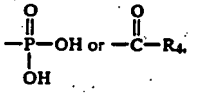
wherein R_1 represents a member selected from the group consisting of H, C_1–C_7 straight or branched alkyl,



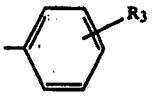
wherein R_3 represents a member selected from the group consisting of —OH, halogen (Cl, Br, I), —OCH_3, —$COOCH_3$, —NO_2 or —$OCOCH_3$; wherein X is -



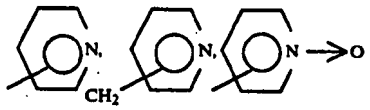
and wherein R_2 represents a member selected from the group consisting of



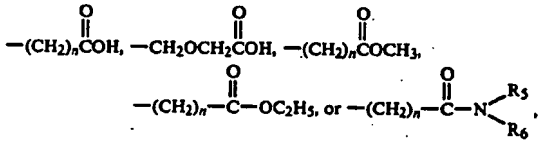
wherein R_4 is a member selected from the group consisting of



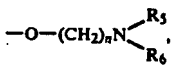
wherein R_3 is defined as above,



the residue of any naturally occurring protein amino acid, the residue of any N- substituted amino acid, wherein said substituent is any amino acid protective group cleavable via hydrogenolysis of hydrolysis (e.g., formyl, benzyloxy, carbonyl, t-butyloxycarbonyl) or the residue of an N,N—C_1—C_5—dialkyl or C_4—C_7 cycloalkylamino acid, or wherein R_4 is a member selected from the group consisting of



wherein n represents an integer of from 1–5 and R_5 and R_6 which may be the same or different represent C_1–C_5 alkyl or together form a heterocyclic ring with the N atom to which they are attached (e.g., pyrolidine, piperidine, morpholine, piperazine, imidazoline, thiazolidine), or wherein R_4 is a member selected from the group consisting of imidazolyl, —O—C_1—C_8 alkyl, —O—benzyl, —O—phenyl, and



wherein n, R_5 and R_6 are defined as above; with the proviso that R in both occurrences cannot represent H simultaneously; or the pharmaceutically acceptable acid addition or basic salts, C_1—C_4 alkylhalide quaternary salts or N-oxide thereof. ;p While all the compounds encompassed within the above generic formula suffice for the applicants' purposes, nevertheless, certain selected compounds are preferred as noted below. A "most" preferred group of compounds is claimed hereinafter.

1. 3-Ethoxycarbonyloxymethyl-diphenylhydantoin.
2. 3-Benzyloxycarbonyloxymethyl-diphenylhydantoin.
3. 3-(2',2',2'-Trichloroethyloxycarbonyloxymethyl)-diphenylhydantoin.
4. 3-(N,N-Dimethylglycyloxymethyl)-diphenylhydantoin.
5. 3-(1-Piperidylacetyloxymethyl)-diphenylhydantoin.
6. 3-Benzoyloxymethyl-diphenylhydantoin.
7. 3-p-Toluyloxymethyl-diphenylhydantoin.
8. 3-Picolinoyloxymethyl-diphenylhydantoin.
9. 3-Nicotinoyloxymethyl-diphenylhydantoin.
10. 3-N-Formylglycyloxymethyl-diphenylhydantoin.
11. 3-Glycyloxymethyl-diphenylhydantoin.
12. 3-N-Benzyloxycarbonylglycyloxymethyl-diphenylhydantoin.
13. 3-Methylsuccinyloxymethyl-diphenylhydantoin.
14. 3-(N,N-Dimethylsuccinamyloxymethyl)-diphenylhydantoin.
15. 3-(N,N-Diethylsuccinamyloxymethyl)-diphenylhydantoin.
16. 3-(N,N,N-Trimethylglycyloxymethyl)-diphenylhydantoin.
17. 3-(N,N,N-Triethylglycyloxymethyl)-diphenylhydantoin.
18. 3-[α-(N,N-Dimethylglycyloxy)ethyl]-diphenylhydantoin.
19. 3-[α-(1-Piperidylacetyloxy)ethyl]-diphenylhydantoin.
20. 3-(α-Benzoyloxyethyl)-diphenylhydantoin.
21. 3-(α-Picolinoyloxyethyl)-diphenylhydantoin.
22. 3-[α-(N-Formylglycyloxy)ethyl]-diphenylhydantoin.
23. 3-[α-(N-Benzyloxycarbonylglycyloxy)ethyl]-diphenylhydantoin.
24. 3-(α-Methylsuccinyloxyethyl)-diphenylhydantoin.
25. 3-[α-(N,N-Dimethylsuccinamyloxy)ethyl]-diphenylhydantoin.
26. 3-[α-(N,N,N-Trimethylglylcyloxy)ethyl]-diphenylhydantoin chloride.
27. 3-(α-Ethoxycarbonyloxybenzyl)-diphenylhydantoin.
28. 3-[α-(N,N-Dimethylglycyloxy)benzyl]-diphenylhydantoin.
29. 3-[α-(1-Piperidylacetyloxy)benzyl]-diphenylhydantoin.
30. 3-(α-Picolinoyloxybenzyl)-diphenylhydantoin.
31. 3-[α-(N-Formylglycycloxy)benzyl]-diphenylhydantoin.
32. 3-[α-(N-Benzyloxycarbonylglycyloxy)benzyl]-diphenylhydantoin.
33. 3-(α-Methylsuccinyloxybenzyl)-diphenylhydantoin.
34. 3-[α-(N,N-Dimethylsuccinamyloxy)benzyl]-diphenylhydantoin.
35. 3-[α-(N,N,N-Trimethylglycyloxy)benzyl]-diphenylhydantoin chloride.
36. 3-(N,N-Dimethylglycylthiomethyl)-diphenylhydantoin.
37. 3-(1-Piperidylacetylthiomethyl)-diphenylhydantoin.
38. 3-p-Toluylthiomethyl-diphenylhydantoin.
39. 3-Picolinoylthiomethyl-diphenylhydantoin.
40. 3-Nicotinoylthiomethyl-diphenylhydantoin.
41. 3-N-Formylglycylthiomethyl-diphenylhydantoin.
42. 3-Glcylthiomethyl-diphenylhydantoin.
43. 3-(N,N-Diethylsuccinamylthiomethyl)-diphenylhydantoin.
44. 3-(N,N,N-Trimethylglycylthiomethyl)-diphenylhydantoin chloride.
45. 3-(N,N,N-Triethylglycylthiomethyl)-diphenylhydantoin chloride.
46. 3-Phosphoryloxymethyl-diphenylhydantoin.
47. 3-Succinyloxymethyl-diphenylhydantoin.
48. 3-Glutaryloxymethyl-diphenylhydantoin.

A "most preferred" group of compounds are claimed hereinafter.

The phrase "non-toxic . . . addition salts" as used herein generally includes the non-toxic acid or basic addition salts of the compounds within the above-described generic formula, formed with non-toxic inorganic and organic acids or bases. For example, the former salts include those derived from inorganic acid such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycollic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, fumaric, toluenesulfonic, methanesulfonate, and the like. The latter salts include those derived from alkali or alkaline earth metal bases or conventional organic bases, e.g., triethylamine, pyridine, piperidine, morpholine, N-methylmorpholine, etc.

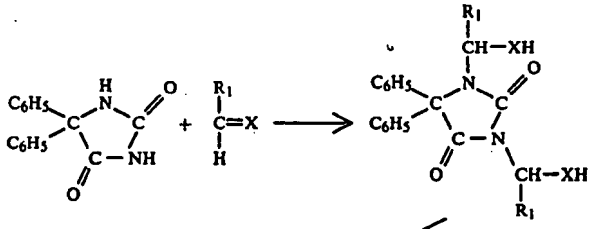
The term "naturally occurring protein amino acid" includes without limitation:

Glycine	Arginine
Alanine	Lysine
Valine	Hydroxylsine
Leucine	Phenylalanine
Isoleucine	Tyrosine
Cysteine	Asparagine
Cystine	Glutamine
Methionine	Proline
Serine	Hydroxyproline
Threonine	Histidine
Aspartic acid	Tryptophan
Glutamic acid	Pyroglutamic acid

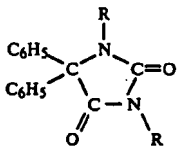
Similarly, the import of the phrase "amino acid protective group 'cleavable' via hydrogenolysis or hydrolysis" can be further gained from a review of U.S. Pat. No. 3,803,120—Felix and U.S. Pat. No. 3,957,803—Bodor, et al.

All the compounds within generic formula (I) are prepared by way of reaction schemes (I) or (II) set out below, wherein R, R_1, R_2 and R_4 are defined as above; and wherein X represents an oxygen, sulfur or nitrogen atom, M represents an alkali or alkaline earth metal (Na, K, Ca, Mg) or thallium, and wherein Y represents a halogen atom, e.g., F, Cl, Br or I. Unless otherwise stated, all reactants are employed in stoichiometric amounts and all reactions are run at standard temperature and pressure.

Reaction Scheme (I)

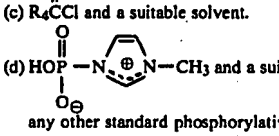


(II) (III) (IV)



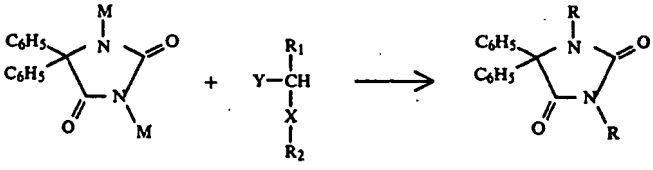
(I)

(a) R_4COH + convenient coupling agent
OR
(b) $R_4COOCOR_4$ and a suitable solvent
OR
(c) R_4CCl and a suitable solvent.



(d) and a suitable solvent, or any other standard phosphorylative procedure.

Reaction Scheme (II)



(VI) (VII) (I)

In reaction scheme (I), the use of a solvent is optional. When desired, however, water is sufficient. When using a coupling agent in the final step of converting the compound of formula (IV) to the final compound of formula (I), any suitable conventional organic coupling agent can be employed. Illustrative of such agents are DCCI or EEDQ. Additional coupling agents can be ascertained from the text entitled *CHEMISTRY OF AMINO ACIDS* (1964), McGraw-Hill. Finally, the reaction for scheme (I) is run at standard temperature and pressure, over a period of from one to 24 hours.

With respect to reaction scheme (II), the reaction is run in a solvent comprising any suitable organic material such as dimethylformamide, ether, halogenated hydrocarbon, etc. The reaction is normally run over a period of from one to 24 hours at standard pressure and at a temperature ranging from room temperature to the boiling point of the solvents selected.

When using either reaction scheme, the final compound of formula (I) can be obtained via standard crystallization procedures, and if necessary, recrystallization can be carried out in the presence of any suitable organic solvent.

In reference to reaction scheme (I), the intermediate compound of formula (IV) is also deemed novel by the applicant, and accordingly, is claimed hereinafter.

The non-toxic pharmaceutically acceptable acid addition salts or acceptable basic salts C_1-C_4 quaternary alkylhalides or N-oxidesof the present invention can be synthesized from the compounds embraced by formula (I) by conventional chemical methods. Normally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess thereof of the desired salt forming inorganic or organic acid or base in a suitable solvent or various combination of solvents. As an example, the free base or acid can be dissolved in an aqueous solution of the appropriate acid or base and the salt recovered by standard techniques, for example, by evaporation of the solution. Alternatively, the free base or acid can be dissolved in an organic solvent such as a lower alkanoyl, an ether, an alkyl ester, or mixtures thereof, for example, methanol, ethanol, ether, ethylacetate, an ethylacetate-ether solution, and the like, whereafter it is treated with the appropriate acid or base to form the corresponding salt. The salt is recovered by standard recovery techniques, for example, by filtration of the desired salt on spontaneous separation from the solution, or it can be precipitated by the addition of a solvent in which the salt is insoluble and recovered therefrom.

The quaternary alkylhalides and N-oxides are prepared in similar fashion by reacting the compound of formula of formula (I) with the corresponding alkylhalide or N-oxide.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the preceding description, utilize the present invention to its fullest extent. Accordingly, the following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the specification and claims in any way whatsoever.

PREPARATION OF THE 3-(HYDROXYMETHYL)DIPHENYLHYDANTOIN PRECURSOR

20 g of 5,5-diphenylhydantoin (0.08 moles) and 80 ml (32 g) of formalin are introduced into a suitable reaction vessel containing 720 ml of water and one g of potassium carbonate. The reaction is stirred at room temperature for 24 hours, after which the subject compound, mp 186.5°–188.5° C., yield 22.58 g (91.86%) is obtained by filtration.

EXAMPLE I-PREPARATION OF SOME SELECTED COMPOUNDS OF FORMULA (I)

PREPARATION OF 3-(N,N-DIMETHYLGLYCYLOXYMETHYL)DIPHENYLHYDANTOIN

Into a suitable reaction vessel containing 5 ml of pyridine, there is added one g (0.0035 mols) of 3-hydroxymethyl-diphenylhydantoin, 0.36 g (0.0035 mols) of N,N-dimethylglycine and 0.79 g (0.0035 mols) of dicyclohexylcarbodiimide (DCCI). The reaction mixture is stirred at room temperature for a period of approximately 24 hours, after which the final product, mp 128°–130°, yield 0.86 g (66.7%) is obtained.

PREPARATION OF 3-(N,N-DIMETHYGLYCYLOXYMETHYL)DIPHENYLHYDANTOIN METHANESULFONATE

Into a suitable reaction vessel containing a sufficient amount of dichloromethane (CH_2Cl_2), there was introduced 0.310 g (0.0032 mols) of methylsulfonic acid (CH_3SO_3H) and 1.18 g (0.0032 mols) of N,N-dimethylglycyloxymethyl-diphenylhydantoin. The reaction mixture was stirred at room temperature overnight after which the subject compound, mp 173°–175° C., yield 2.25 g (92.6%) was obtained.

PREPARATION OF 3-(N,N-DIMETHYLGLYCYLOXYMETHYL)DIPHENYLHYDANTOIN SALICYLATE

By following the immediately preceding reaction scheme but substituting a stoichiometric amount of salicyclic acid for methysulfonic acid, the subject compound was obtained in quantatative yield.

PREPARATION OF 3-(GLUTARYLOXYMETHYL)DIPHENYLHYDANTOIN

To a suitable reaction vessel containing 25 ml of pyridine, there was added 10 g (0.0354 mols) of 3-hydroxymethyldiphenyldydantoin and 4.85 g (0.0425 mols) of glutaric anhydride. The reaction mixture was stirred at room temperature for 5 days, thus obtaining the subject compound, mp 137.5°–146° C., yield 7.90 g (56.0%).

PREPARATION OF 3-(SUCCINYLOXYMETHYL)DIPHENYLHYDANTOIN

To a suitable reaction vessel containing 25 ml of pyridine, there was added 10 g (0.0354 mols) of 3-hydroxymethyldiphenylhydantoin and 4.25 g (0.0425 mols) of succinyl anhydride. The reaction mixture was stirred at room temperature for 5 days after which the subject compound, mp 141.5°–146° C. yield 8.36 g (62.0%) was obtained.

In similar fashion, the remaining compounds of the present invention can be prepared with similar success by merely following the preceding examples and substituting the generically and/or specifically described reactants and/or operating conditions of this invention for those of the preceding examples.

The improved solubility of the novel compounds of the instant invention is demonstrated via 3-(N,N-dimethylglycyloxymethyl)diphenylhydantoin methanesulfonate, a selective compound from within formula (I). The compound was added in increments to water until solubility was determined. The solubility for the subject

compound was in excess of 100 mg/ml which is quite dramatic when compared to the solubility of the parent scale, diphenylhydantoin per se, i.e., less than 0.02 mg/ml (approximate 5,000 fold increase in aqueous solubility over diphenylhydantoin).

When repeating the above-described solubility experiment, but this time, employing the remaining compounds of formula (I), substantially improved solubility characteristics over diphenylhydantoin are observed.

The novel and useful diphenylhydantoin compounds of this invention can be used by the pharmaceutical and the veterinary arts for their antiepileptic, anticonvulsant and antiarrhythmic effects in a variety of pharmaceutical or veterinary preparations In these preparations, the new compounds are administrable in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable form. The pharmaceutical or veterinary preparation which contains the compound is conveniently admixed with a nontoxic pharmaceutical organic carrier or a nontoxic pharmaceutical inorganic carrier, usually about 0.01 mg up to 2500 mg, or higher per dosage unit. Typical of pharmaceutically acceptable carriers are, for example, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid, and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like, as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

Exemplary of a typical method for preparing a tablet containing the active agents is to first mix the agent with a nontoxic binder such as gelatin, acacia mucilage, ethyl cellulose, or the like. The mixing is suitably carried out in a standard V-blender and usually under anhydrous conditions. Next, the just prepared mixture can be slugged through conventional tablet machines and the slugs fabricated into tablets. The freshly prepared tablets can be coated, or they can be left uncoated. Representative of suitable coatings are the nontoxic coatings including shellac, methylcellulose, carnauba wax, styrene-maleic acid copolymers, and the like. For oral administration, compressed tablets containing 0.01 milligram, 5 milligrams, 25 milligram, 50 milligrams, etc., up to 2500 milligrams are manufactured in the light of the above disclosure and by art known fabrication techniques well known to the art and set forth in Remington's Pharmaceutical Science, Chapter 39, Mack Publishing Co., 1965. The pharmaceutical manufacture of a formulation is shown in Example II.

EXAMPLE II

Ingredients:	Per tablet, mg.
3-(N,N-dimethylglycyloxymethyl)-diphenylhydantoin methanesulfonate	50.0
Cornstarch	15.0
Cornstarch paste	4.5
Calcium carbonate	15.0
Lactose	67.0
Calcium stearate	2.0
Dicalcium phosphate	50.0

To formulate the tablet uniformly blend the active compound, cornstarch, lactose, dicalcium phosphate and calcium carbonate under dry conditions in a conventional V-blender until all the ingredients are uniformly mixed together. Next, the cornstarch paste is prepared as a 10% paste and it is blended with the just prepared mixture until a uniform mixture is obtained. The mixture is then passed through a standard light mesh screen, dried in an anhydrous atmosphere and then blended with calcium stearate, and compressed into tablets, and coated if desired. Other tablets containing 10, 50, 100, 150 mgs, etc., are prepared in a like fashion.

EXAMPLE III

Ingredients:	Per tablet, mg.
3-(N,N-dimethylglycyloxymethyl)diphenylhydantoin methanesulfonate	50.0
Cornstarch	15.0
Cornstarch paste	4.5
Calcium carbonate	15.0
Lactose	67.0
Calcium stearate	2.0
Dicalcium phosphate	50.0

The manufacture of capsules containing 10 milligrams to 2500 milligrams for oral use consists essentially of mixing the active compound with a nontoxic carrier and enclosing the mixture in a polymeric sheath, usually gelatin or the like. The capsules can be in the art known soft form of a capsule made by enclosing the compound in intimate dispersion within an edible, compatible carrier, or the capsule can be a hard capsule consisting essentially of the novel compound mixed with a nontoxic solid such as talc, calcium stearate, calcium carbonate, or the like. Exemplary of a typical use for employing a capsule containing 100 mg of 3-(N,N-dimethylglycyloxymethyl)diphenylhydantoin methanesulfonate for use as therapeutically indicated ad libitum for antiepileptic effects. Capsules containing 25 mg, 75 mg, 125 mg, and the like, of the novel compounds, singularly or mixtures of two or more of the novel compounds are prepared, for example, as follows:

EXAMPLE IV

Ingredients:	Per capsule, mg.
Active compound of formula (I)	50.0
Calcium carbonate	100.0
Lactose, U.S.P.	200.0
Starch	130.0
Magnesium stearate	4.5

The above ingredients are blended together in a standard blender and then discharged into commercially available capsules. When higher concentrations of the active agent is used, a corresponding reduction is made in the amount of lactose.

The dose administered, whether a single dose, multiple dose, or a daily dose, will of course, vary with the particular compound of the invention employed because of the varying potency of the compound, the

chosen route of administration, the size of the recipient and the nature of the arrythmia or epileptic seizure and other states characterized by involuntary movements such as Parkinson's syndrome. The dosage administered is not subject to definite bounds, but it will usually be an effective amount, or the equivalent on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active drug to achieve its desired pharmacological and physiological effects. The dosage administered for the management of cardiac arrythmias, grand mal, petit mal, psychomoter equivalent seizures and other forms of convulsive seizures is for mammals, including primates and humans a general oral dose of 200 to 300 mg daily, with the oral dose of normally 100 mg up to 4 times a day; the usual intravenous dose of 100 to 350 mg, followed by if indicated 100 to 150 mg at a later period, and the usual intramuscular dose of 100 to 300 mg every 6 to 8 hours, with 3 to 4 injections per day. For household animals, such as dogs, the administrable dose is about 30 to 200 mg about every 6 to 8 hours.

For administering to valuable household animals, such as dogs, or for administering to laboratory animals such as mice, for scientific studies, the compound is prepared in the form of an injectable, or in the form of a food premix, such as mixing with dry meal, mash and the like, and then the prepared premix is added to the regular feed, thereby administering the compound to the domestic or laboratory animal.

The novel therapeutic compounds of the invention can also be formulated into compositions comprising other compounds useful in the sympotomatic therapy of cardiac arrhthmias, epilepsy and other states characterized by involuntary movements such as chorea and Parkinson's syndrome. For example, 3-(N,N-dimethylglycyloxymethyl)diphenylhydantoin methanesulfonate, can be mixed with 5,5-diphenyl-2,4-imidazolidinedione for oral administration at the rate of 200 mg to 600 mg daily, for example, as adminstered in capsule form. Typical capsules comprise 15 mg or 50 mg of 3-(N,N-dimethylglycyloxymethyl)diphenylhydantoin methanesulfonate and 15 mg or 50 mg of 5,5-diphenyl-2,4-imidazolidinedione for oral administration up to 4 times a day.

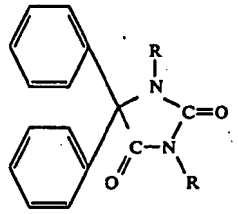
The novel and useful hydantoates of the invention are adaptable for administration for their physiological antiepileptic and anticonvulsant effects from drug delivery systems, such as skin delivery systems, gastrointestinal drug delivery devices, and the like, wherein the delivery device is manufactured from naturally occurring and synthetic polymeric materials. Representative of materials acceptable for the fabrication of drug delivery systems containing the compounds for controlled drug administration include materials such as polyvinyl chloride, polyisoprene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, polydimethylsiloxane, hydrophillic hydrogels of esters of acrylic and methacrylic acid, polyvinyl acetates, propylenevinyl acetate copolymers, and the like.

It is also quite obvious that due to the extremely exceptional solubility characteristics of the claimed compounds over diphenylhydantoin per se and derivatives of the prior art, superior parenteral formulation and administration is achieved. Similarly, improved oral bioavailability is achieved owing to the increased solubility of the subject compounds.

From the foregoing description, it is obvious that one of ordinary skill in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and/or modifications to the invention for adapting it to various usages and conditions. As such, these changes and modifications are properly, equitably and intended to be, within the full range of equivalence of the following claims.

What we claim is:

1. A 5,5-diphenylhydantoin compound having the structural formula:



wherein each R is independently selected from the group consisting of hydrogen and $—CH(R_1)—O—P(O)(OH)_2$, wherein R_1 is selected from the group consisting of hydrogen and C_1–C_7 straight or branched chain alkyl; with the proviso that the R's cannot simultaneously be hydrogen; or the pharmaceutically acceptable acid addition or basic salts, C_1–C_4 alkylhalide quaternary salts or N-oxide thereof.

2. The compound as defined by claim 1, wherein either R is hydrogen, with the other being $—CH(R_1)—O—P(O)(OH)_2$.

3. The compound as defined by claim 1, same being 3-phosphoryloxymethyl-5,5-diphenylhydantoin.

* * * * *

EXHIBIT 4
IND SUBMISSION LETTER

American Critical Care

American Hospital Supply Corporation

1600 Waukegan Road
McGaw Park IL USA 60085

Telephone 312 473-3000
Cable ARSTOLAB
TLX 6871516 AMCRC UW

March 31, 1986

Food and Drug Administration
Division of Neuropharmacologic Drug Products (HFN 120)
Document Control Room 10B-34
5600 Fishers Lane
Rockville, MD 20857

Gentlemen:

Accompanying this letter, and submitted in triplicate, is an IND for ACC-9653 injection. ACC-9653 injection is a specifically formulated solution of a novel prodrug of phenytoin. The rationale for development of ACC-9653 injection, an anticonvulsant agent, is to eliminate the serious limitations of the current drug of choice for treatment of status epilepticus, phenytoin sodium.

Although treatment of status epilepticus is usually initiated with diazepam, the therapeutic effectiveness of diazepam is limited by its rapid distribution and its use must be followed by administration of another, longer-acting anticonvulsant such as phenytoin sodium. Continuous infusion of diazepam is not practical due to potential development of respiratory depression, hypotension, and depressed mental function.

Drawbacks of phenytoin sodium include incompatibility with intravenous infusion solutions, the formulation's alkalinity (pH 12) and the components of the formulation. Phenytoin sodium, injected intramuscularly, has been shown to crystallize in muscle. Due to its high pH, phenytoin sodium causes pain, swelling and irritation at the site of injection and may cause subcutaneous injury if extravasated. Due to its incompatibility with most diluents, direct intravenous administration of phenytoin sodium is recommended in the labeling. However, rapid IV administration of undiluted phenytoin sodium injection has been reported to cause serious complications, including fatal cardiac arrest and respiratory arrest. In addition, to avoid onset of heart block and hypotension, the rate of IV infusion of phenytoin sodium has been limited to a maximum of 50 mg/min. Slower IV administration of undiluted phenytoin sodium is inconvenient as it takes significant time to administer larger doses and this procedure requires close supervision of an experienced clinical practitioner.

Preclinical pharmacology testing, reported in the accompanying IND, demonstrated that ACC-9653 is rapidly and completely converted to free phenytoin following intravenous infusion in rats and dogs, with a half-life of less than four minutes. Preclinical toxicology tests indicate that ACC-9653 injection causes no significant venous or perivascular irritation, compared with phenytoin sodium injection. No local or systemic adverse effects not related to phenytoin were observed.

ACC-9653 Injection represents a formulation of phenytoin which is soluble in intravenous solutions, without solvents such as propylene glycol, and which allows rapid infusion. Because of the several unique properties of ACC-9653 Injection, American Critical Care is proposing an accelerated clinical development program for this drug. Therefore, we believe it is essential that we meet with the Division as early as possible to discuss our projected program and the basis for its evolution. I will contact Mr. Purvis after you have had an opportunity to complete your administrative review of our IND, with our request to schedule a conference.

We appreciate your prompt attention to our Notice.

Yours truly,

Jack Waterman

John H. Waterman
Manager, Product Registration

JHW:bd

EXHIBIT 5
IND ACKNOWLEDGMENT LETTER

File pro-DPH IND

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 14, 86

IND 28,217

American Critical Care
attention: John H. Waterman
1600 Waukegan Road
McGaw Park, Illinois 60085

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 28,217

Sponsor: American Critical Care

Name of Drug: ACC-9653 Injection

Date of Submission: March 31, 1986

Date of Receipt: April 4, 1986.

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

RECEIVED
APR 17 1986
REGULATORY AFFAIRS

U.S. GOVERNMENT PRINTING OFFICE: 1984 - 436-677/7217

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

Should you have any questions concerning this IND, please call: Mr. David Banks.

Consumer Safety Officer
(301) 443- 3800

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Bureau of Drugs, HFD-120
Attention: DOCUMENT CONTROL ROOM # 10B-30
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Marion C. Cayton
John S. Pilcher

Supervisory Consumer Safety Officer
Division of Neuropharmacological
Drug Products
Bureau of Drugs

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228c (1/82)

U.S. GOVERNMENT PRINTING OFFICE: 1984 - 436-676/7225

EXHIBIT 6
NDA SUBMISSION LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company

DATE OF SUBMISSION
July 14, 1994

ADDRESS (Number, Street, City, State and Zip Code)
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

TELEPHONE NO. (Include Area Code)
313/996-7756
FAX 313/998-2856

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-450

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
fosphenytoin sodium

PROPRIETARY NAME (if any)
Cerebyx®

CODE NAME (if any)
CI-982

CHEMICAL NAME
5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

DOSAGE FORM
Sterile Solution

ROUTE OF ADMINISTRATION
Injection

STRENGTH(S)
75 mg/ml

PROPOSED INDICATIONS FOR USE

Epilepsy

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATIONS:

IND 28,217

Drug Master Files:

Drug Product
Parke-Davis Sterile Products Operation DMF 3579
Division of Warner-Lambert Company
870 Parkedale Road
Rochester, MI 48307

Container and Closure System
The West Company DMF 1546

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION (Check one)

☐ PRESUBMISSION
☒ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one).*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

July 14, 1994

NDA 20-450
Ref. No. 1
Cerebyx® (fosphenytoin sodium)

Re: Original New Drug Application

Food and Drug Administration
Document and Records Section
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir/Madam:

Pursuant to 21 CFR 314.50 enclosed is a New Drug Application (NDA) for Cerebyx® (fosphenytoin sodium) for use in the treatment of epilepsy. The NDA number for Cerebyx was preassigned on February 10, 1994.

As required under the Prescription Drug User Fee Act of 1992, 50% of the 1994 application fee ($81,000) has been sent to the Food and Drug Administration in care of Mellon Bank Philadelphia, Pennsylvania on June 29, 1994.

Please note that while the actual number of volumes in the archival copy of this submission is 93, the volumes are only numbered up to 92 because there is a volume 7 and 7a. Review copies of each technical section are also provided with this NDA submission.

Patent and exclusivity information and the Generic Drug Enforcement Act Certification are in Item 13, contained in Volume 1 of this NDA. Please refer to the attached Form FDA 356h and NDA Index which detail the complete contents of this NDA.

Pursuant to 21 CFR 314.440, a copy of the Chemistry, Manufacturing and Controls section of this NDA has been sent to the FDA District Office in Detroit, Michigan, since the drug substance and drug product are manufactured in Michigan.

The original IND (28,217) for fosphenytoin sodium was filed by American Critical Care on March 31, 1986 and transferred to Parke-Davis on March 27, 1990. This IND is under the auspices of the Division of Neuropharmacological Drug Products. Fosphenytoin received orphan drug designation for the treatment of patients with status epilepticus of the grand mal type on June 4, 1991.

Sections of the proposed Cerebyx package insert included with this NDA contain information taken directly from the current parenteral Dilantin® package insert. We are updating the current Dilantin package insert and will be submitting these proposed revisions to the parenteral Dilantin package insert in the near future. After revisions in the parenteral Dilantin package insert have been approved by FDA, we will submit to this NDA those changes that impact the Cerebyx package insert.

Because Cerebyx offers significant therapeutic gain over currently available parenteral therapy for the treatment of status epilepticus, we request that this NDA receive a priority review.

If you need additional information or have any questions regarding this submission, please contact me at 313-996-7426 or FAX 313-996-7890.

Sincerely,

Janeth L. Turner, R.N., B.S.N.
Director
Worldwide Regulatory Affairs

JT/rp
m:\fosph\62994.1

Attachments

cc: Mr. Gary Lloyd, Newark District Office (letter only)
Ms. Heather Pederson, Newark District Office (letter only)
Mr. John P. Dempster, Detroit District Office (Volumes 2 - 7a)

EXHIBIT 7
NDA RESUBMISSION LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company

DATE OF SUBMISSION
February 22, 1995

ADDRESS (Number, Street, City, State and Zip Code)
2800 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

TELEPHONE NO. (Include Area Code)
313/996-7426
FAX 313/998-3283

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-450

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
fosphenytoin sodium

PROPRIETARY NAME (if any)
Cerebyx®

CODE NAME (if any)
CI-982

CHEMICAL NAME
5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt

DOSAGE FORM
Sterile Solution

ROUTE OF ADMINISTRATION
Injection

STRENGTH(S)
75 mg/ml

PROPOSED INDICATIONS FOR USE

Epilepsy

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATIONS:

IND 28,217

Drug Master Files:

Drug Product
Parke-Davis Sterile Products Operation DMF 3579
Division of Warner-Lambert Company
870 Parkedale Road
Rochester, MI 48307

Container and Closure System
The West Company DMF 1546

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION (Check one)

RESUBMISSION
☐ ORIGINAL APPLICATION

☐ AN AMENDMENT TO A PENDING APPLICATION
☒ RESUBMISSION

☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one).*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

February 22, 1995

NDA 20-450
User Fee ID No. 2566
Ref. No. 7
Cerebyx® (fosphenytoin sodium) Injection

Re: Resubmission of Original New Drug Application (Volume 3.1 to 3.15)

Paul D. Leber, M.D.
Director
Division of Neuropharmacological
Drug Products (HFD-120)
Document Control Room 4037
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Center 2
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Leber:

Reference is made to the Cerebyx® (fosphenytoin sodium) Injection NDA 20-450, submitted to FDA on July 15, 1994, and to FDA's letter of September 12, 1994 notifying us of their refusal to file this NDA. Reference is also made to the background refusal to file meeting material submitted to FDA on October 6, 1994 (NDA Ref. No. 4, Volume 2.1); to our December 8, 1994 meeting with FDA to discuss the refusal to file; and to our minutes of this meeting submitted to FDA on December 16, 1994 (NDA Ref. No. 6). At that meeting, it was agreed that the NDA was fileable with the patient numbers as outlined in the background meeting material and with the formate level data as provided in the background meeting material.

Pursuant to 21 CFR 314.50, enclosed is our updated New Drug Application (NDA) for Cerebyx for use in the treatment of epilepsy. As agreed to with Mr. Robbin Nighswander, CSO, HFD-120, because this NDA is a resubmission of our July 15, 1994 NDA, only those sections of the NDA that have been updated are included in this submission. Thus while the July 15, 1994 NDA contains 93 volumes, this resubmission contains only 15 volumes. As discussed with Mr. Robbin Nighswander, the volumes in the July 15, 1994 NDA are identified as 1.1 to 1.92, while the volumes in this updated NDA are identified as 3.1 to 3.15. The NDA index in Volume 3.1 of this resubmission identifies, in one column, the location in the July 1994 NDA of those NDA documents that are to be taken from the July 1994 submission and cross-referenced to this submission. The second column identifies the location of those NDA documents that are enclosed. All documents in the resubmitted NDA are immediately preceded by a "Note to FDA Reviewer" which identifies how the document has been revised from that submitted in the July 15, 1994 NDA.

Patent and exclusivity information updated as per the General Agreements in Tariffs and Trade (GATT) and the Generic Drug Enforcement Act Certification are in Item 13, contained in Volume 3.1 of this NDA.

As required under the Prescription Drug User Fee Act of 1992, 50% of the 1995 application fee ($104,000) has been sent to the Food and Drug Administration in care of Mellon Bank, Philadelphia, Pennsylvania on February 17, 1995. A copy of the User Fee cover sheet is attached.

Pursuant to 21 CFR 314.440, an identical copy of the Chemistry, Manufacturing, and Controls section as submitted in this updated NDA has been sent to the FDA District Office in Detroit, Michigan, as the drug substance and the drug product are manufactured in Michigan.

Parke-Davis received orphan drug designation for fosphenytoin for the treatment of patients with status epilepticus of the grand mal type on June 4, 1991.

Sections of the proposed Cerebyx package insert included with this NDA contain information taken directly from the current parenteral Dilantin package insert. A proposed revised parenteral Dilantin package insert was submitted to NDA 10-151 on January 25, 1995 (NDA Supplement S-033). After revisions in the parenteral Dilantin package insert have been approved by FDA, we will submit to the Cerebyx NDA those changes that impact the Cerebyx package insert.

Because Cerebyx offers significant therapeutic gain over currently available parenteral therapy for the treatment of status epilepticus, we request that this NDA receive a priority review.

If you need additional information or have any questions regarding this submission, please contact me at 313/996-7426 or FAX 313/998-3283.

Sincerely,

Janeth L. Turner, R.N., B.S.N.
Director
Worldwide Regulatory Affairs

JT/rp
m:\cerebyx\21695.7

Attachments

cc: Mr. Carl C. Reynolds, FDA District Office, Detroit, Michigan (cover letter; Vol. 3.2 - 3.7)

EXHIBIT 8
IND LOG

FDA CONTACT

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04072	Thu, Apr 17, 1986 J. Purois J. Waterman	Record of FDA contact RE: Verbal request for meeting Request meeting with FDA to discuss clinical plan.
B04072	Tue, Apr 29, 1986 D. Banks J. Waterman	Record of FDA contact RE: Verbal request for meeting Additional request for meeting with FDA to discuss clinical plan.
B04072	Wed, Apr 30, 1986 D. Banks J. Waterman	Record of FDA contact RE: IND initiation decision Telephone conversation from FDA relaying IND initiation decision.
B04072	Thu, May 01, 1986 P. Hanson J. Waterman	Record of FDA contact RE: Study plans FDA inquiry regarding protocol plans.
B04072	Fri, May 02, 1986 D. Banks J. Waterman	Record of FDA contact RE: Verbal suggestions FDA suggestion for addition to the Gerber protocol.
B04072	Wed, May 07, 1986 C. Berninger J. Waterman	Record of FDA contact RE: Request for information
B04072	Mon, Jan 12, 1987 D. Banks J. Waterman	Record of FDA contact RE: Request meeting to discuss clinical plan Telephone conversation with FDA requesting meeting to discuss clinical plan.
B04072	Mon, Jan 26, 1987 D. Banks J. Waterman	Record of FDA contact RE: Request meeting to discuss clinical plan Telephone conversation with FDA requesting meeting to discuss clinical plan.
B04088	Thu, Oct 29, 1987 K. Osekey Meyer	Record of FDA contact RE: Request for Infomation FDA requested status on PR. 9653-86-2.

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Wed, Jul 11, 1990 S. Decorte	Record of FDA contact RE: CI-982 receipt of meeting package Acknowledgement of receipt of meeting package.
B04073	Tue, Aug 14, 1990 S. Decorte	Record of FDA contact RE: Confirm teleconference Confirm teleconference date
B04073	Wed, Aug 07, 1991 M. Mille J. Conover	Record of FDA contact RE: To seek FDA guidance on the nature of our development
B04073	Thu, Aug 08, 1991 M. Mille J. Conover	Record of FDA contact RE: To inform us that FDA wants to meet to discuss our stro To inform us that FDA wants to meet to discuss our stroke program.
B04073	Thu, Sep 05, 1991 M. Mille J. Conover	Record of FDA contact RE: To inquire about deferred consent for status epilepticus s To inquire about deferred consent for status epilepticus studies.
B04073	Tue, Sep 17, 1991 S. Decorte J. Conover	Record of FDA contact RE: To discuss meeting/teleconference with Dr. Katz on the i
B04073	Fri, Sep 27, 1991 R. Katz J. Conover	Record of FDA contact RE: To discuss informed vs. deferred consent issues for clinic
B04073	Thu, Nov 21, 1991 M. Mille J. Conover	Record of FDA contact RE: Notification of tentative meeting date for stroke indicatio
B04073	Wed, Nov 27, 1991 S. Decorte J. Conover	Record of FDA contact RE: To obtain date of meeting with FDA for anticonvulsant in To obtain date of meeting with FDA for anticonvulsant indication.

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Mon, Dec 02, 1991 K. Higgins J. Conover	Record of FDA contact RE: To schedule stroke anticonvulsant meetings
B04073	Mon, Dec 16, 1991 M. Mille J. Conover	Record of FDA contact RE: To identify FDA staff and consultants for the stroke and
B04073	Wed, Jan 08, 1992 K. Higgins J. Conover	Record of FDA contact RE: To discuss FDA attendees at 16-Jan anticonvulsant meet
B04073	Wed, Jan 08, 1992 M. Mille J. Conover	Record of FDA contact RE: To discuss FDA attendees at 15-Jan stroke meeting
B04073	Fri, Mar 13, 1992 N. Chamberlain R. Spivey	Record of FDA contact RE: Determine status of FDA minutes for 16-Jan-92 meeting CSO will check on status of 16-Jan-92, meeting minutes.
B04073	Tue, Mar 17, 1992 N. Chamberlain R. Spivey	Record of FDA contact RE: Check on status of minutes from FDA meeting of 16-Jan
B04073	Thu, Jul 09, 1992 N.Chamberlain B. Scott	Record of FDA contact RE: Ascertain status of 7-May scientific literature submission
B04073	Thu, Aug 13, 1992 B. Scott R. Baweja	Record of FDA contact RE: Status of 982-24/Retention of Samples
B04073	Wed, Sep 16, 1992 B. Scott N. Chamberlain	Record of FDA contact RE: Reviewed outstanding submissions Reviewed theree (3) outstanding submissions with FDA.

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Tue, Oct 13, 1992 B. Scott N. Chamberlain	Record of FDA contact RE: Review status of requests for information Review status on three (3) outstanding requests for information.
B04073	Mon, Jan 11, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Follow-up on request to speak with the fosphenytoin ch Follow-up on request to speak with the fosphenytoin chemical reviewer.
B04073	Mon, Jan 11, 1993 N. Chamberlain B. Scott	Record of FDA contact RE: To identify the fosphenytoin chemical reviewer so that w
B04073	Fri, Jan 15, 1993 M. Gruzewska P. Chen	Record of FDA contact RE: To inform us that she needs more time to respond to the
B04073	Tue, Jan 26, 1993 N. Chamberlain B. Scott	Record of FDA contact RE: Identify date for pre-NDA meeting Meeting date tentatively set for 8-Mar.
B04073	Wed, Jan 27, 1993	Record of FDA contact RE: To make sure FDA did not expect us to give a presentati
B04073	Wed, Jan 27, 1993 N. Chamberlain B. Scott	Record of FDA contact RE: Confirm our attendance of the FDA's 8-Mar Pre-NDA me Confirmed attendance at the 8-Mar meeting at FDA from 1:00 - 2:30 pm.
B04073	Wed, Mar 10, 1993	Record of FDA contact RE: Request overheads and abstract from 982-24

SubType: IND

Cl#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Mon, May 03, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Determine if FDA would like us to pursue providing Cana
B04073	Fri, May 14, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Relay FDA opinion of fosphenytoin as a NCE
B04073	Mon, May 24, 1993 V. Hale M. Eldon	Record of FDA contact RE: Request fosphenytoin pharmacokinetic data; begin colla
B04073	Tue, May 25, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Inform FDA that we had submitted the minutes of the M
B04073	Thu, Jun 10, 1993 V. Hale J. Turner	Record of FDA contact RE: Discuss collaborative review of fosphenytion pharmacoki
B04073	Thu, Jun 17, 1993 V. Hale J. Turner	Record of FDA contact RE: Inform FDA that we will provide them with the draft da
B04073	Wed, Jun 23, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Request complete copy of protocol 982-22
B04073	Wed, Jun 30, 1993 Hale/Ludden/McCor J. Turner	Record of FDA contact RE: Discuss design and results of 982-018 and review fosph

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Fri, Jul 09, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Request FDA to schedule a pre-NDA environmental asses
B04073	Mon, Jul 19, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Discuss environment assessment (EA) meeting and FDA
B04073	Wed, Aug 18, 1993 N. Chamberlain J. Turner	Record of FDA contact RE: Determine status of our request for a pre-NDA environm
B04073	Fri, Aug 20, 1993 P. Vincent S. Brennan	Record of FDA contact RE: Fosphenytoin environmental assessment
B04073	Wed, Oct 06, 1993 N. Chamberlain J. Turner	Record of FDA contact :
B04073	Tue, Oct 12, 1993 V. Hale J. Turner	Record of FDA Contact Correct submission of October 8, 1993
B04073	Tue, Oct 19, 1993 J. Turner N. Chamberlain	Record of FDA Contact Determine acceptable time frame for a pre-NDA Environmental Assessment Meeting.
B04073	Tue, Nov 02, 1993 J. Turner N. Chamberlain	Record of FDA Contact Cancel tentative November 30 pre-NDA environmental assessment meeting.
B04073	Fri, Nov 12, 1993 S. Blum S. Brennan	Record of FDA Contact

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Fri, Nov 12, 1993 J. Turner N. Chamberlain	Record of FDA Contact Schedule fosphenytoin environmental assessment pre-NDA meeting.
B04073	Thu, Nov 18, 1993 N. Chamberlain J. Turner	Record of FDA contact re: carcinogenicity studies & request for meeting minutes
B04073	Tue, Nov 23, 1993 J. Turner N. Chamberlain	Record of FDA Contact Carcinogenicity testig for the NDA.
B04073	Wed, Dec 01, 1993 N. Chamberlain J. Turner	Record of FDA Contact Pre-meeting materials for December 6, 1993 meeting.
B04073	Thu, Jan 20, 1994 J. Turner V. Hale	Record of FDA Contact: Request comupter disk of additional PK data.
B04073	Wed, Mar 23, 1994 N. Chamberlain J. Turner	Record of FDA contact: Determine status of FDA minutes of January 16, 1992 and There are no FDA minutes of the January 1992 meeting. FDA will not have minutes of the March 1993 meeting available prior to our NDA submission.
B04073	Thu, Apr 28, 1994 J. Turner V. Hale	Record of FDA Contact: Request PD comments and approval of abstract on fosphen
B06976	Thu, May 19, 1994 J. Turner V. Hale	Record of FDA Contact: Send PD a final copy of the abstract as sent to AAPS. Dr. Hale mailed the attached note and abstract to me. She has also given Ms. Nancy Chamberlain (CSO) a copy of the abstract for file.
B04073	Fri, May 27, 1994 J. Turner G. Fitzgerald	Record of FDA Contact: Request IND listings for mutagenicity studies. In response to Dr. Fitzgerald's request, I instructed her as to where in the IND the mutagenicity assays were located (IND Ref. No. and date of submission)

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Fri, May 27, 1994 J. Turner G. Fitzgerald	Record of FDA Contact: Request extra copies of mutagenicity reports.
B04073	Thu, Jul 14, 1994 Heather Pederson D. Furlano	Determine whether Newark required a filed copy of NDA CMC (as well as Detroit Dist
B04073	Thu, Aug 18, 1994 Thomas Ludden Jeff Koup	Request information on population pharmacokinetic parameters for phenytoin
B04073	Mon, Aug 29, 1994 Martha Heimann P. Chen	To request the type II DMF number for Phenytoin because it is used as the starting m
B04073	Wed, Sep 21, 1994 Paul Leber W. M. Merino	Fosphenytoin NDA refuse-to-file letter.
B04073	Thu, Apr 06, 1995 John Feeney Irwin G. Martin, Ph.D	Question on protocol 982-26
B04073	Mon, Jun 12, 1995 Robbin Nighswander Janeth L. Turner	3-day IND Safety Report
B04073	Fri, Jul 07, 1995 John Feeney, MD Janeth L. Turner	Determine if additional follow up information is available for the IND safety report of

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Date / To: / From:	RE/Contents
B04073	Fri, Apr 12, 1996 Merril Mille Janeth L. Turner	3-day telephone report of an adverse event
B04073	Tue, Apr 16, 1996 Merril Mille Janeth L. Turner	Discuss logistics of 3-Day Adverse Event telephone reports
B04073	Tue, Jun 25, 1996 John Feeney, MD Janeth L. Turner	Request additional information on protocols submitted to the IND (982-28, pediatric P

FDA CORRESPONDENCE

IND/NDA/DMF#: 28,217 | IND | Doc Type: FDA CORrespondence | 9/16/96 | Page 1

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04074	0	Mon, Mar 31, 1986	Initial IND Submission
B04074	0	Mon, Mar 31, 1986	Initial IND - Submitted by American Critical Care
B04083		Mon, Apr 14, 1986	FDA Letter RE: Acknowledging Receipt (IND 28,217) Acknowledgement of receipt of IND on 4-Apr-86; number 28,217 assigned.
B04083		Mon, May 19, 1986	FDA Letter RE: Clinical Study Notification to proceed with study.

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04083		Tue, Sep 16, 1986	FDA Letter Regarding Transfer to Du pont
			Transfer of IND 28, 217 ACC-9653 (phenytoin prodrug) from American Critical Care, American Hospital Supply Corp., a wholly-owned subsidiary of Baxter-Travenol Laboratories, Inc., Deerfield, IL to Du Pont Critical Care, Inc., subsidiary of E.I. Du Pont De Nemours and Co. Inc., Wilmington, DE. Du Pont Critical Care, Inc. hereby accepts sponsorship of IND 28,217.
		J. Waterman	
B04083		Fri, Nov 14, 1986	Protocol Amendment (New Investigators)
			PR. 9653-086-003:
B04084		Wed, Dec 03, 1986	Information Amendment (Pharmacology/Toxicology)
			(5) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04072		Wed, Feb 25, 1987	Safety Report
			Patient: #None (JDB) Ohio State University AE: 2 syncopal episodes
B04086		Fri, Apr 03, 1987	Protocol Amendment (Change in Protocol & New Investigators)
B04086		Mon, Apr 27, 1987	Protocol Amendment (New Investigators)
			Pr. 9653-086-002:
B04086		Wed, Jun 10, 1987	Protocol Amendment (New Investigators)
			Pr. 9653-086-005-001:
B04086		Tue, Jul 14, 1987	Protocol Amendment (New Investigators)
			PR. 9653-086-005-004:

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04087		Wed, Aug 05, 1987	Protocol Amendment (New Investigators)
			PR. 9653-086-005-003:
B04087		Fri, Aug 14, 1987	Protocol Amendment (New Investigators)
			PR. 9653-086-005-002:
B04088		Tue, Oct 13, 1987	Protocol Amendment (New Investigators)
			PR. 9653-087-007:
B04088		Fri, Nov 20, 1987	Protocol Amendment (New Investigators)
			PR. 9653-087-011:
B04089	9	Tue, Jan 05, 1988	Annual Report
			Cutoff Date: 19-May-87
B04090	10	Fri, Jun 24, 1988	Protocol Amendment (New Investigators)
			PR. 9653-087-009-001:
B04091	11	Mon, Aug 01, 1988	Annual Report
			Cutoff Date: 19-May-88
B04099	12	Wed, Jan 11, 1989	Protocol Amendment (New Investigators)
			PR. 9653-087-010
B04100	13	Fri, Feb 02, 1990	Letter RE: IND Transfer from Du Pont Critical Care to Du Pont De Nemours
		P. Leber	Transference of IND from Du Pont Critical Care, Inc. to E.I. Du Pont De Nemours & Co.
B04100	14	Thu, Mar 29, 1990	Annual Report
			Cutoff Date: 09-May-90
B04100	15	Fri, Mar 30, 1990	Letter RE: Transfer of Sponsorship from Du Pont to Parke-Davis
		P. Leber, MD	CI-980 - Effective 27-Mar-90; Du Pont transferred IND 28,217 to Parke-Davis

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B04100	16	Tue, May 08, 1990 P. Leber	Letter RE: IND Transfer of Sponsorship Parke-Davis has assumed sponsorship of IND for 28,217.
B04100	17	Tue, Jun 12, 1990 P. Leber	Letter RE: Request Meeting
B04100	18	Thu, Aug 09, 1990 P. Leber	Letter RE: General Correspondence CI-982: Attachment of 6 pages which were omitted from submission of 12-Jun-90 (SN #017).
B04100	19	Thu, Dec 06, 1990	Minutes of FDA Meeting
B04100	20	Thu, Dec 06, 1990	IB Update Date: 16-Nov-90 RR # X-720-02846 Authors: S.J. Lobbestael/J.G. Marriott
B04100	21	Mon, Feb 04, 1991 P. Leber	Letter RE: Request for Information Request copy of FDA's minutes of 29-Aug-90 teleconference meeting.
B04100		Tue, Feb 12, 1991	Memo to File: Minutes of FDA Teleconference (29-Aug-90)
B04100	22	Tue, Feb 19, 1991 P. Leber	Letter RE: Investigator's Brochure (1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04100	23	Tue, Feb 19, 1991	Protocol Amendment (New Investigators) PR. 982-012-000:

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04101	24	Mon, Apr 01, 1991	Information Amendment (Pharmacology/Toxicology)
			(60) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04113	25	Mon, Apr 01, 1991	Information Amendment (Pharmacology/Toxicology)
			(1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04114	26	Mon, Apr 22, 1991	Letter RE: Information Amendment (Clinical)
B04114	27	Fri, Apr 26, 1991	Annual Report
			Issue Date: 24-Apr-91
B04114	28	Thu, May 02, 1991	Letter RE: Information Amendment (Pharmacology/Toxicology)
		P. Leber	
B04115	29	Thu, May 02, 1991	Protocol Amendment (New Investigator)
			PR. 982-013-013:

SubType: IND

CI#: 982 | Sub Date: 3/31/86

Generic: | Appr Date:

Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04115	30	Thu, May 16, 1991		Protocol Amendment (New Investigator & Change in Protocol)
B04115	31	Thu, May 23, 1991		Protocol Amendment (New Investigators) PR. 982-013-002: PR. 982-013-005: PR. 982-013-006: PR. 982-013-011:
B04115	32	Thu, Jun 06, 1991		Protocol Amendment (New Investigators) PR. 982-013-004:
B04115	33	Mon, Jun 17, 1991		Protocol Amendment (New Investigators) PR. 982-014-006: PR. 982-013-001:
B04115	34	Tue, Jun 25, 1991		Protocol Amendment (New Investigators) PR. 982-013-006: C. Roberts, LPN/M.L. Donnan, RN PR. 983-013-007: H. Bonnette, MD/L. Frighetti, RN/P. Segal PR. 983-013-011: D. Miller, RN
B04115	35	Tue, Jul 02, 1991		Protocol Amendment (New Investigators) PR. 982-014-002: PR. 982-014-007: PR. 982-013-008:
B04115	36	Tue, Jul 09, 1991		Information Amendment (Pharmacology/Toxicology) (2) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.

SubType: IND

CI#: 982 | Sub Date: 3/31/86

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04116	37	Tue, Jul 16, 1991	Protocol Amendment (New Investigators) PR. 982-014-001: PR. 982-014-005: PR. 982-013-012:
B04116	38	Fri, Jul 19, 1991 P. Leber J. Conover	Letter RE: IND Safety Report: Initial Written Report
B04116	39	Tue, Jul 23, 1991	Protocol Amendment (New Investigators) PR. 982-014-009:
B04116	40	Tue, Jul 30, 1991	Protocol Amendment (New Investigators) PR. 982-014-004: PR. 982-014-008: PR. 982-013-008: J.R. Desmarais, RN/N.L. Johnson, RN, BSN
B04116	41	Tue, Jul 30, 1991	Information Amendment (Pharmacology/Toxicology) (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04116	42	Tue, Aug 06, 1991	Protocol Amendments (New Investigators & Change in Protocol)

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No:
B04116	43	Tue, Aug 20, 1991	Information Amendment (Pharmacology/Toxicology)
			(2) Research Reports submitted. Refer to Research Report list for RR #, date, author and title
B04116	44	Thu, Oct 03, 1991	Letter RE: Request for Meeting
		P. Leber	
		J. Conover	
B04116	45	Thu, Oct 03, 1991	Letter RE: Request for Meeting
		P. Leber	
		J. Conover	
B04116	46	Thu, Oct 10, 1991	Protocol Amendment (New Investigators)
			PR. 982-013-007: F.R. Mestas,MD/S.R. Zellner, MD
B04116	47	Thu, Oct 31, 1991	Information Amendment (Pharmacology/Toxicology)
			(1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04116	48	Thu, Nov 14, 1991	Information Amendment (Pharmacology/Toxicology)
			(3) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.

SubType: IND

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04116	49	Tue, Dec 03, 1991	Protocol Amendment (New Investigators) PR. 982-020-000:
B04116	50	Fri, Dec 20, 1991	Letter RE: Meeting Agenda
B04116	51	Fri, Dec 20, 1991	Letter RE: Meeting Agenda - New Protocol
B04117	52	Thu, Feb 06, 1992	Protocol Amendment (Change in Protocol & New Investigators)
B04117	53	Thu, Feb 13, 1992	Information Amendment (Pharmacology/Toxicology) (2) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.

SubType: IND

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04117	54	Wed, Apr 22, 1992	Minutes of FDA Meeting
B04117	55	Wed, May 06, 1992	Protocol Amendment (New Investigators)
B04117	56	Thu, May 07, 1992 P. Leber B. Scott	Letter RE: General Correspondence

SubType: IND

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04117	57	Tue, May 19, 1992	Letter RE: Information Amendment (CMC)
B04118	58	Fri, Jun 05, 1992	Protocol Amendment (Change in Protocol)
B04118	60	Tue, Jun 09, 1992	Protocol Amendment (New Investigators) PR. 982-015-009:
B04118	59	Tue, Jun 09, 1992 P. Leber B. Scott	Letter RE: General Correspondence
B04119	63	Thu, Jun 11, 1992	Information Amendment (Pharmacology/Toxicology) (1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.

SubType: IND

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04118	62	Thu, Jun 11, 1992	Information Amendment (Pharmacology/Toxicology)
			(6) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04118	61	Thu, Jun 11, 1992 P. Leber S. Brennen	Letter RE: Information Amendment (CMC)
B04119	64	Thu, Jun 25, 1992 P. Leber B. Scott	Letter RE: Information Amendment
B04119	65	Fri, Jun 26, 1992	Annual Report
			Issue Date: 26-Jun-92 Reporting Period: 6-Mar-91 through 9-Mar-92
B04119	66	Tue, Jul 07, 1992	Protocol Amendment (New Investigators)
			PR. 982-015-003:
B04119	67	Fri, Jul 17, 1992	Protocol Amendment (New Investigators)
			PR. 989-024-000:

SubType: IND

CI#: 982 | Sub Date: 3/31/86

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04119	68	Thu, Jul 23, 1992 P. Leber B. Scott	Letter RE: General Correspondence
B04119	69	Mon, Aug 10, 1992 P. Leber B. Scott	Protocol Amendment (New Protocol & Change in Protocol)
B04119	70	Thu, Aug 13, 1992 P. Leber B. Scott	Protocol Amendment (New Protocol/New Investigators/Change in Protocol)
B04119	71	Mon, Aug 24, 1992 P. Leber B. Scott	Protocol Amendment (Change in Protocol/New Investigators)

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04119	72	Tue, Aug 25, 1992 P. Leber B. Scott		Protocol Amendment (New Protocol for Review)
B04119	73	Mon, Aug 31, 1992		Protocol Amendment (Change in Protocol)
B04119	74	Thu, Sep 03, 1992		Protocol Amendment (Change in Protocol)
B04119	75	Thu, Sep 17, 1992		Protocol Amendment (New Investigators) PR. 982-016-006: R. Kriel, MD/F. Langendorf, MD
B04119	76	Thu, Sep 24, 1992		Protocol Amendment (New Investigators) PR. 982-016-010: F.B. Carlton, MD
B04119	77	Wed, Sep 30, 1992		Protocol Amendment (New Investigators) PR. 982-022-002: G.L. Barkley, MD

SubType: IND

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04119	78	Wed, Oct 07, 1992	Protocol Amendment (Change in Protocol & New Investigators)
B04120	79	Mon, Oct 12, 1992	Information Amendment (Pharmacology/Toxicology & Clinical) (8) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04124	80	Mon, Oct 19, 1992	Protocol Amendment (New Investigators) PR. 982-016-009: F. Matsuo, MD
B04124	81	Tue, Oct 27, 1992	Protocol Amendment (New Investigators) PR. 982-016-013: B. Uthman, MD
B04124	82	Thu, Nov 12, 1992	Protocol Amendment (New Investigators) PR. 982-016-001: B. Alldredge, PharmD/A. Gelb, MD
B04124	83	Mon, Nov 23, 1992	Protocol Amendment (New Investigators) PR. 982-016-005: T. Turnbull, MD
B04124	84	Fri, Dec 18, 1992	Protocol Amendment (New Investigators) PR. 982-016-013: J. Malone, MD/M. Childress, MD PR. 982-015-005: C. Bryan, RN PR. 982-021-003: F. Sharbrough, MD/T. Lagerlund, MD PR. 982-016-009: D. Kim, MSN, RN
B04124	85	Mon, Jan 04, 1993	Protocol Amendment (New Investigators) PR. 982-022-004:

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Product Name:	Fosphenytoin Sodium Parenteral		

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04124	86	Wed, Jan 13, 1993 P. Leber P. Chen	Letter RE: CMC Amendment
B04124	87	Mon, Jan 25, 1993	Protocol Amendment (New Investigators & Change in Protocol)
B04124	88	Wed, Feb 10, 1993 P. Leber P. Chen	Information Amendment (CMC)

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04124	89	Thu, Feb 18, 1993	Pre-NDA Meeting - March 8
B04124	90	Fri, Feb 26, 1993	Protocol Amendment (New Investigators & Change in Protocol)
B04124	91	Thu, Mar 04, 1993	Information Amendment (Pharmacology/Toxicology) (1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04124	92	Thu, Mar 11, 1993 P. Leber J. Turner	Response to FDA Request for Information
B04124	93	Fri, Mar 26, 1993	Protocol Amendment (New Investigator) PR. 982-016: C. Lai, MD
B04124	94	Thu, Apr 15, 1993	Protocol Amendment (Change in Protocol)

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04124	95	Mon, May 24, 1993 P. Leber J. Turner	Letter RE: General Correspondence
B04124	96	Tue, May 25, 1993	Protocol Amendment (New Investigators) PR. 982-016-011:
B05829	97	Thu, Jun 17, 1993	Information Amendment (Pharmacology/ToxicologyJ) (1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B05908	98	Mon, Jun 21, 1993 P. Chen	Information Amendment (CMC)

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B05908	99	Wed, Jun 23, 1993		General Correspondence
B05908	100	Thu, Jun 24, 1993		General Correspondence
B05908	101	Tue, Jun 29, 1993 P. Leber J. Turner		Response to FDA Request for Information
B05908	102	Fri, Jul 09, 1993	Issued Date: 9-Jul-93 Reporting Period: 10-Mar-92 through 3-May-93 Complete report 25 pages	Annual Report

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06147	103	Thu, Jul 15, 1993		Information Amendment (Clinical)
				(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B06235	104	Thu, Jul 29, 1993		Request for Environmental Assessment Pre-NDA Meeting
		J. Turner		
B06242	105	Mon, Aug 16, 1993		Information Amendment (Pharmacology/Toxicology)
				(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B06329	106	Wed, Sep 22, 1993		Information Amendment: Clinical
		P. Leber		
		J. Turner		
B06330	107	Fri, Oct 01, 1993		Protocol Amendment: Change in Protocol
		P. Leber		982-016 - Filed 9/17/92 (Ser. No. 075) - Amendment 1
		J. Turner		
B06330	108	Fri, Oct 08, 1993		Response to FDA Request for Information
		P. Leber		
		J. Turner		

SubType: IND

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B06330	109	Wed, Oct 20, 1993 N. Chamberlain J. Turner	Response to FDA Request for Information Attached as requested in our telephone conversation of today, is an extra desk copy of our July 29, 1993 submission (Serial No. 104), requesting a FDA pre-NDA meeting to discuss the Environmental Assessment for the fosphenytoin NDA.
B06376	110	Fri, Oct 22, 1993 P. Leber J. Turner	Information Amendments: Clinical (4) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B06510	111	Mon, Nov 29, 1993 P. Leber J. Turner	Pre-Meeting Materials: Proposed Environmental Assessment

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06510	112	Fri, Dec 10, 1993		Information Amendment: CMC
		P. Leber		
		P. Chen		
B06734	113	Fri, Jan 21, 1994		Information Amendments: Pharm/Tox/Clinical
		P. Leber		(5) Research Reports Submitted See Research Report LIst for RR#, date, author, title
		J. Turner		
B06736	114	Wed, Mar 23, 1994		Protocol Amendment: Change in Protocol
		P. Leber		
		J. Turner		

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06976		Tue, May 31, 1994 G. Fitzgerald J. Turner	(4) Toxicology Reports were sent to Glenna Fitzgerald (FDA)	
B06976	115	Thu, Jul 21, 1994 P. Leber J. Turner	Annual Report	
B06976	116	Mon, Aug 29, 1994 P. Leber P. Chen	Information Amendment: Chemistry, Manufacturing, and Controls	

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B07491	117	Wed, Feb 08, 1995 P. Leber J. Turner	Information Amendments: Clinical Investigator's Brochure submitted See Research Report list for RR#, date, author, title
B07491	118	Fri, Mar 31, 1995 P. Leber J. Turner	Protocol Amendment: New Protocol
B07491	119	Thu, Apr 20, 1995 P. Leber J. Turner	Protocol Amendment: Change in Protocol, New Investigators
B07491	120	Thu, May 11, 1995 P. Leber J. Turner	Protocol Amendment: New Protocol

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B07491	121	Tue, May 16, 1995 P. Leber J. Turner	New Sites 9 and 10
B07491	122	Wed, Jun 21, 1995 P. Leber J. Turner	Initial Written Report
B10269	123	Thu, Jul 20, 1995 P. Leber J. Turner	Annual Report Attached for your information and files is our Annual Report dated July 20, 1995 for IND 28,217, Fosphenytoin Sodium Injection.
B10269	124	Tue, Aug 01, 1995 P. Leber J. Turner	Protocol Amendment: New Investigators The following centers were added to Protocol 982-026: 982-026-003, 982-026-004 and 982-026-007. Addendum C was submitted for Protocol 982-026, applying only to center 001
B10269	125	Mon, Aug 07, 1995 P. Leber J. Turner	Information Amendment: Clinical

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B10269	126	Tue, Aug 08, 1995	Protocol Amendment: New Investigators
		P. Leber	Regarding Protocol 982-026: Amendment 1
		J. Turner	
B10269	127	Fri, Jan 19, 1996	Protocol Amendments: New Investigators
		P. Leber	Additional investigators to 982 protocols
		J. Turner	
B10269	128	Fri, Mar 08, 1996	General Correspondence: Request for Review of Pediatric Protocol
		P. Leber	
		J. Turner	
B10269	129	Tue, Mar 12, 1996	IND Safety Report: Initial Written Report
		P. Leber	Adverse Event No. 001-0982-960011. Also submitted for IND 40,588 #020.
		J. Turner	
B10269	130	Mon, Apr 22, 1996	IND Safety Report: Initial Written Report
		P. Leber	Adverse Event No. 002-0982-960001
		J. Turner	
B10269	131	Tue, Apr 30, 1996	IND Safety Report: Follow-up to a Written Report
		P. Leber	
		J. Turner	
B16683	132	Wed, May 22, 1996	Protocol Amendment: New Protocol
		P. Leber	New Protocol 982-029, New Center 982-029-017: R. Leroy, M.D.
		J. Turner	
B16683	133	Wed, Jun 12, 1996	IND Safety Report: Follow-up to a Written Report
		P. Leber	
		J. Turner	

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B16683	134	Wed, Jul 10, 1996	Protocol Amendment: New Protocol, New Investigators
		P. Leber	New Protocol 982-028: New Center 982-028-001 Regarding Protocol 982-029: New Centers 982-029-001, 982-029-009, 982-029-014 and 982-029-015.
		J. Turner	
B16683	135	Thu, Aug 01, 1996	Annual Report
		P. Leber	Annual Report
		J. Turner	
B16683	136	Fri, Aug 02, 1996	IND Safety Report: Initial Written Report
		P. Leber	
		J. Turner	
B16683	138	Tue, Aug 13, 1996	Response to FDA Request for Information
		P. Leber	
		J. Turner	

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Product Name: Fosphenytoin Sodium Parenteral

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B16683	137	Tue, Aug 13, 1996	General Correspondence: Phase IV Commitment, Meeting Request, Change in Protocol
		P. Leber	
		J. Turner	
B21241	139	Thu, Aug 15, 1996	Protocol Amendment: New Investigators
		P. Leber	
		J. Turner	
	140	Wed, Sep 11, 1996	Protocol Amendment: New Investigators
		P. Leber	Regarding Protocol 982-028: New Center 982-028-002 Regarding Protocol 982-029: New Centers 982-029-006 and 982-029-019.
		J. Turner	

IND RESEARCH REPORTS

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref Barcode	RR Number: Sub Date	RR Date	Author/ Title
	RR T9653-017		M. E. Lewandowski
B04084	12/3/86	12/3/86	"Determination of the Local Irritation Effects of ACC-9653 and Phenytoin After Intramuscular Injection of Rabbits"
	RR T9653-018		M. E. Lewandowski
B04084	12/3/86	12/3/86	"Acute Toxicity of ACC-9653 and Phenytoin in Rats by Intramuscular Injection"
	RR T9653-019		M. E. Lewandowski
B04084	12/3/86	12/3/86	"Determination of the Determination of the Local Irritation Effects of AC-9653 and Phenytoin After Daily Intramuscular Injection in Rabbits for Five Consecutive Days"
	RR T9653-020		M. E. Lewandowski
B04084	12/3/86	12/3/86	"Determination of the Local Irritation Effects of ACC-9653 and Phenytoin After Daily Intramuscular Injection in Rabbits for Five Consecutive Days"
	RR T9653-022		M. E. Lewandowski
B04084	12/3/86	12/3/86	"Determination of the Maximum Tolerated Dose (MTD) of AC-9653 and Phenytoin by Intramuscular Injection in Dogs"
0	RR CPDM-9653-85-03		J. J. Miceli/J. R. Koup
B04081	5/1/85	3/31/86	"Pharmacokinetics and Bioavailability of Phenytoin and Bioequivalence of ACC-9653 to Phenytoin Sodium After Intravenous Administration of ACC-9653 in Dogs"
0	RR CPDM-9653-85-04		C. Y. Quon
B04081	5/1/85	3/31/86	"In Vitro Hydrolysis of ACC-9653 by Human, Dog and Rat Blood and Tissues"
0	RR 100-86-00427		B. S. Brown et al
B04082	3/1/86	3/31/86	"Comparative Study of the Effects of ACC-9653 and Phenytoin on Maximal Electroshock Seizures in the Mouse"
0	RR 100-86-00428		B. S. Brown et al
B04082	3/1/86	3/31/86	"Comparison of the Antiarrhythmic Activity of ACC-9653 and Phenytoin in Cardiac Glycoside-Induced Arrhythmias In Vitro and In Vivo"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author / Title
0 / B04082	RR 100-86-00429	3/31/86	J. E. Shaffer et al "Effects of ACC-9653 and Phenytoin on Guinea Pig Right and Left Atria"
0 / B04081	RR CPDM-9653-85-05	3/31/86	C. M. Lai, et al "Pharmacokinetics and Relative Bioavailability of Phenytoin After Intramuscular Administration of Phenytoin Sodium and ACC-9653 in Dogs"
0 / B04081	RR CPDM-9653-85-06	3/31/86	Y. C. Chan et al "Tissue Distribution Study of 14C-ACC-9653 in Rats"
0 / B04081	RR CPDM-9653-85-07	3/31/86	C. M. Lai et al "Mass Balance Study of Intravenously Administered 14C-ACC-9653 in Rats"
0 / B04081	RR CPDM-9653-85-09	3/31/86	C. M. Lai et al "Pharmacokinetics and Absolute Bioavailability of ACC-9653 and Phenytoin After Intravenous and Intramuscular Administration of ACC-9653 in Dogs"
0 / B04080	RR T9652-007	3/31/86	M. E. Lewandowski "Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Beagle Dogs"
0 / B04077	RR T9652-002	3/31/86	M. Blair "Two Week Intravenous Toxicity Study of ACC-9653 in Dogs"
0 / B04075	RR T9653-001	3/31/86	M. Blair "Two Week Intravenous Toxicity Study of ACC-9653 in Rats"
0 / B04079	RR T9652-003	3/31/86	R. W. Maher "Seven Day Intravenous Dose-Ranging Study With ACC-9653 in CD Rats"

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Ser# Ref Barcode	RR Number: Sub Date/RR Date		Author/ Title
0	RR T9652-009		M. E. Lewandowski
B04080	3/20/86	3/31/86	"Determination of the Maximum Tolerated Dose (MTD) of ACC-9653 and Phenytoin by Intravenous Infusion in Rabbits"
0	RR T9652-010		M. E. Lewandowski
B04080	3/20/86	3/31/86	"Acute Toxicity of ACC-9653 and Phenytoin in Mice by 30-Minute Intravenous Infusion"
0	RR T9652-011		M. E. Lewandowski
B04080	3/20/86	3/31/86	"Acute Toxicity of ACC-9653 and Phenytoin in Weanling Rats by 30-Minute Intravenous Infusion"
0	RR T9652-016		M. E. Lewandowski
B04080	3/20/86	3/31/86	"CNS Evaluation of ACC-9653 and Phenytoin in Mice"
0	RR T9652-004		R. W. Maher
B04079	3/21/86	3/31/86	"Seven Day Intravenous Dose-Ranging Study With ACC-9653 in Beagle Dogs"
0	RR T9652-005		M. E . Lewandowski
B04079	3/21/86	3/31/86	"Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Rats by Bolus Injection"
0	RR T9652-006		M. E. Lewandowski
B04080	3/21/86	3/31/86	"Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin by 30-Minute Infusion in Rats"
0	RR T9652-008		M. E. Lewandowski
B04080	3/21/86	3/31/86	"Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Beagle Dogs by 30-Minute Infusion"
0	RR T9652-012		M. E. Lewandowski
B04080	3/21/86	3/31/86	"Acute Toxicity of ACC-9653 and Phenytoin in Neonate Rats by Intraperitoneal Injection"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	/ RR Date	Author / Title
0	RR T9652-013		M. E. Lewandowski
B04080	3/24/86	3/31/86	"Acute Toxicity of ACC-9653 and Phenytoin in Adult Rats by Intraperitoneal Injection"
0	RR T9652-014		M. E. Landowski
B04080	3/24/86	3/31/86	"Comparison of the Venous and Perivascular Irritation of ACC-9653 and Sodium Phenytoin Formulations in Rabbits"
1	RR 764-01615		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"HPLC-UV Assay of ACC-9653 in Dog Plasma"
1	745-02092		L.A. Dostal
B06734	10/22/93	7/14/94	"Intramuscular Fertility and General Reproduction Study in Female Rats with CI-982"
1	745-02101		D.K. Monteith
B06734	11/2/93	7/14/94	"In Vitro Structural Chromosome Aberration Assay of CI-982 in V79 Chinese Hamster Lung Cells"
1	764-02035		L.L. Radulovic
B06734	12/15/93	7/14/94	"Phenytoin Toxicokinetics in Male and Female Beagle Dogs Following Single 50- mg/kg Fosphenytoin (CI-982) IM and IV Doses"
22	RR-X 720-02847		J. Hughes/S.J. Lobbestael
B04100	1/21/91	2/19/91	"Investigator's Brochure: Fosphenytoin Sodium (CI-982)"
24	RR 744-00024		J.J. Miceli/J.R. Koup
B04111	1/18/91	4/1/91	"A Dose Ranging Tolerance Study of CI-982 in Healthy Volunteers: A Single Center Study, 9653-86-01"
24	RR 744-00025		J.J. Miceli/J.R. Koup
B04111	1/18/91	4/1/91	"Absolute Bioavailability of Phenytoin After Intravenous CI-982 Administration of Healthy Male Volunteers, 9653-86-02"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref Barcode	RR Number: Sub Date/RR Date		Author/ Title
24	RR 744-00026		J.J. Miceli/J.R. Koup
B04111	1/18/91	4/1/91	"Safety and Tolerance to Increasing Infusion Rates of CI-982 Administration as a Bolus Dose to Healthy Volunteers, 9653-86-05"
24	RR 744-00027		J.J. Miceli/J.R. Koup
B04111	1/18/91	4/1/91	"Evaluation of Phenytoin Levels After IM and IV CI-982 Administration in Epileptic Patients on Chronic Oral Dilantin Monotherapy, 9653-86-05"
24	RR 744-00028		J.J. Miceli/J.R. Koup
B04111	1/18/91	4/1/91	"Absolute Bioavailability of Phenytoin After Intramuscular CI-982 Administration to Healthy Male Volunteers, 9653-86-06"
24	RR 744-00029		J.J. Miceli/J.R. Koup
B04112	1/18/91	4/1/91	"Conversion of CI-982 to Phenytoin to Patients With Renal or Hepatic Disease Compared to Healthy Subjects - A Pilot Study, 9653-87-07"
24	RR 744-00030		J.J. Miceli/J.R. Koup
B04112	1/18/91	4/1/91	"Absolute Bioavailability of Phenytoin From CI-982 in Patients With Therapeutic Serum Phenytoin Concentrations Using Stable Isotope Techniques 9653-87-10"
24	RR 744-00031		J.J. Miceli/J.R. Koup
B04112	1/18/91	4/1/91	"Evaluation of the Pharmacokinetic Interaction Between Diazepam and CI-982 in Healthy Male Volunteers, 9653-87-11"
24	RR 745-01596		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Simultaneous HPLC-UV Assay of Phenytoin and the Para- and Meta- Hydroxy Metabolites of Phenytoin in Whole Blood"
24	RR 764-01597		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"In Vitro Hydrolysis of ACC-9653 by Human, Dog and Rat Blood and Tissues"
24	RR 764-01598		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"HPLC/UV Assay of Phenytoin Prodrug in Whole Blood"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref Barcode	RR Number: Sub Date	RR Date	Author/ Title
24	RR 764-01600		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Tissue Distribution Study of 14C-ACC-9653 in Rats"
24	RR 764-01601		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Pharmacokinetics and Relative Bioavailability of Phenytoin After Intramuscular Administration of Phenytoin Sodium and ACC-9653 in Dogs"
24	RR 764-01603		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Standard Assay Procedure for HPLC Determination of Phenytoin in Blood"
24	RR 764-01604		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Standard Assay Procedure for HPLC Determination of Phenytoin Prodrug in Blood"
24	RR 764-01605		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Preclinical Drug Metabolism Summary for ACC-9653"
24	RR 764-01606		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Pharmacokinetics and Bioavailability of Phenytoin and Bioequivalence of ACC-9653 to Phenytoin Sodium After Intravenous Administration of ACC-9653 in Dogs"
24	RR 764-01608		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Mass Balance Study of IV Administered 14C-ACC-9653 in Rats"
24	RR 764-01609		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Pharmacokinetics and Absolute Bioavailability of ACC-9653 and Phenytoin After Intravenous and Intramuscular Administration of ACC-9653 in Dogs"
24	RR 764-01610		J.J. Miceli/J.R. Koup
B04110	1/18/91	4/1/91	"Comparative Pharmacokinetics and Bioavailability of Phenytoin After Oral Administration of Phenytoin Sodium Capsule and Intramuscular Administration of ACC-9653 in Dogs"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author/ Title
24 / B04110	RR 764-01611 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Distribution and Hydrolysis of Intramuscular ACC-9653 and Phenytoin Sodium"
24 / B04110	RR 764-01612 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Determination of Blood Levels of ACC-9653 and Phenytoin in Rats After Intramuscular Administration of ACC-9653 or Phenytoin"
24 / B04110	RR 764-01613 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "HPLC-UV Assay of Phenytoin in Dog Muscle Homogenate"
24 / B04110	RR 764-01614 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "HPLC-UV Assay of ACC-9653 in Dog Muscle Homogenate"
24 / B04110	RR 764-01616 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Simultaneous HPLC-UV Assay of Phenytoin and the Para- and Meta- Hydroxy Metabolites of Phenytoin in Dog Plasma and Urine"
24 / B04110	RR 764-01618 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Comparative Pharmacokinetics and Bioavailability of Phenytoin After Intramuscular Phenytoin Sodium, Oral Phenytoin Sodium, and Oral ACC-9653 in Dogs"
24 / B04110	RR 764-01619 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Single and Multiple-Dose Pharmacokinetics of Phenytoin and ACC-9653 After Simultaneous Intramuscular Administration of Phenytoin Sodium and ACC-9653 in Dogs"
24 / B04110	RR 764-01620 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Plasma Protein Binding Interaction of ACC-9653 and Carbamazepine, Diazepam, Phenobarbital, Phenytoin and Valproic Acid"
24 / B04110	RR 764-01622 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Preclinical Drug Metabolism Summary for ACC-9653"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author / Title
24 / B04110	RR 764-01623 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Standard Assay Procedure for HPLC Determination of ACC-9653 in Human Urine"
24 / B04110	RR 764-01624 / 1/18/91	4/1/91	J.J. Miceli/J.R. Koup "Standard Assay Procedure for Simultaneous HPLC Determination of Phenytoin, 5-(P-Hydroxyphenyl)-5-(Phenylhydantoin) (P-HPPH) and 5-(M-Hydroxyphenyl) -5-(Phenylhydantoin (M-HPPH) in Human Urine"
24 / B04101	RR 745-01720 / 2/4/91	4/1/91	M.E. Lewandowski "Acute Toxicity of ACC-9653 and Phenytoin in Neonate Rats by Intraperitoneal Injection"
24 / B04101	RR 745-01721 / 2/4/91	4/1/91	M.E. Lewandowski "Determination of the Maximum Tolerated Dose (MTD) of ACC-9653 and Phenytoin by Intravenous Infusion in Rabbits"
24 / B04101	RR 745-01722 / 2/4/91	4/1/91	M.E. Lewandowski "Acute Toxicity of ACC-9653 and Phenytoin in Mice by 30-Minute Intravenous Infusion"
24 / B04101	RR 745-01723 / 2/4/91	4/1/91	M.E. Lewandowski "Acute Toxicity of ACC-9653 and Phenytoin in Adult Rats by Intraperitoneal Injection"
24 / B04101	RR 745-01724 / 2/4/91	4/1/91	M.E. Lewandowski "Comparison of the Venous and Perivasclar Irritation of ACC-9653 and Sodium Phenytoin Formulations in Rabbits"
24 / B04101	RR 745-01725 / 2/4/91	4/1/91	M.E. Lewandowski "Acute Toxicity of ACC-9653 and Phenytoin in Weanling Rats by 30-Minute Intravenous Infusion"
24 / B04101	RR 745-01726 / 2/4/91	4/1/91	M.E. Lewandowski "Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Rats by Bolus Infusion"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author / Title
24 / B04101	RR 745-01727 / 2/4/91	4/1/91	M.E. Lewandowski "Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin by 30-Minute Infusion in Rats"
24 / B04101	RR 745-01728 / 2/4/91	4/1/91	M.E. Lewandowski "Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Beagle Dogs"
24 / B04102	RR 745-01729 / 2/4/91	4/1/91	M.E. Lewandowski "Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Beagle Dogs by 30-Minute Infusion"
24 / B04102	RR 745-01730 / 2/4/91	4/1/91	R.W. Maher "Seven Day Intravenous Dose-Ranging Study With ACC-9653 in CD Rats"
24 / B04102	RR 745-01731 / 2/4/91	4/1/91	R.W. Maher "Seven Day Intravenous Dose-Ranging Study With ACC-9653 in Beagle Dogs"
24 / B04102	RR 745-01732 / 2/4/91	4/1/91	R.W. Maher "Two Week Intravenous Toxicity Study of ACC-9653 in Rats"
24 / B04104	RR 745-01733 / 2/4/91	4/1/91	R.W. Maher "Two Week Intravenous Toxicity Study of ACC-9653 in Dogs"
24 / B04105	RR 745-01734 / 2/4/91	4/1/91	R.W.Maher "Cardiovascular Toxicity Evaluation of ACC-9653 and Phenytoin in Beagle Dogs"
24 / B04105	RR 745-01734 / 2/4/91	4/1/91	M.E. Lewandowski "Determination of the Presence of Gluocosuria After Intravenous Infusion of ACC-9653 and Phenytoin in Rats"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author / Title
24 / B04105	RR 745-01735	4/1/91	M.E. Lewandowski "CNS Evaluation of ACC-9653 and Phenytoin in Mice"
24 / B04105	RR 745-01737	4/1/91	M.E. Lewandowski "Determination of the Local Irritation Effects of ACC-9653 and Phenytoin After Intramuscular Infection of Rabbits"
24 / B04105	RR 745-01738	4/1/91	M.E. Lewandowski "Acute Toxicity of ACC-9653 and Phenytoin in Rats by Intramuscular Injection"
24 / B04105	RR 745-01739	4/1/91	R.W. Maher "Fourteen Day Intramuscular Dose-Ranging Toxicity Study With ACC-9653 in Beagle Dogs"
24 / B04106	RR 745-01740	4/1/91	R.W. Maher "Thirteen Week Intramuscular Injection Toxicity Study of ACC-9653 in Dogs"
24 / B04107	RR 745-01741	4/1/91	M.E. Lewandowski "Determination of the Local Irritation Effects of AC-9653 and Phenytoin After Daily Intramuscular Injection in Rabbits for Five Consecutive Days"
24 / B04107	RR 745-01742	4/1/91	M.E. Lewandowski "Determination of the Maximum Tolerated Dose (MTD) of AC-9653 and Phenytoin by Intramuscular Injection by Dogs"
24 / B04107	RR 745-01743	4/1/91	M.E. Lewandowski "Determination of Blood Levels of ACC-9653 and Phenytoin in Rats After Intramuscular Administration of ACC-9653 of Phenytoin"
24 / B04107	RR 745-01744	4/1/91	R.W. Maher "Thirteen Week Intramuscular Injection Toxicity Study of ACC-9653 in Rats"

SubType: IND

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref Barcode	RR Number: Sub Date/RR Date		Author/ Title
24	RR 745-01745		R.W. Maher
B04109	2/4/91	4/1/91	"Fourteen Day Intramuscular Dose-Range Study With ACC-9653 in CD Sprague Dawley Rats"
24	RR 745-01746		M.E. Lewandowski
B04109	2/4/91	4/1/91	"In Vitro Effect of an ACC-9653 Formulation and a Sodium Phenytoin Formulation on Human Blood"
24	RR 745-01786		J.R. Herman/J.R Koup
B04109	3/4/91	4/1/91	"Assessment of the Potential Risks Associated With Systemic Formaldehyde"
25	RR 745-01786		J.R. Herman/J.R. Koup
B04113	3/4/91	4/1/91	"Assessment of the Potential Risks Associated With Systemic Formaldehyde"
36	RR 745-01843		J. A. Petrere
B04115	6/18/91	7/9/91	"Exploratory Intravenous Study in Rats with CI-982"
36	RR 745-01844		J. A. Petrere
B04115	6/18/91	7/9/91	"Exploratory Intravenous Study in Rabbits with CI-982"
41	RR 740-02970		M.G. Vartanian/C.P. Taylor
B04116	6/17/91	7/30/91	"Effects of Fosphenytoin on NMDA-Medicated Neurodegeneration in Rat Pups"
43	RR 764-01636		C.S. Krcmarik et al
B04116	6/4/91	8/20/91	"Validated Liquid Chromatographic Assay for Fosphenytoin (CI-982) in Human Plasma"
43	RR 764-01703		C.S. Krcmarik et al
B04116	7/17/91	8/20/91	"Validated Liquid Chromatographic Assay for Fosphenytoin (CI-982) in Human Urine"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author/ Title
47 / B04116	RR 740-02986 / 10/3/91	10/31/91	J.J. Cordon et al "Dose-Response Effects of Fosphenytoin in the Middle Cerebral Artery Occlusion (MCAO) Model of Focal Stoke in Rats"
48 / B04116	RR 745-01871 / 9/30/91	11/14/91	J.A. Petrere "Intravenous Dose Range-Finding Study in Pregnant Rabbits With CI-982"
48 / B04116	RR 740-02988 / 10/3/91	11/14/91	J. Cordon/P. Boxer "The Effects of Fosphenytoin on Infarct Size and Neurological Deficits in a Proximal Middle Cerebral Artery Occlusion Model in Rats"
48 / B04116	RR 740-02989 / 10/3/91	11/14/91	J. Cordon/P. Boxer "The Effects of Fosphenytoin as a Neuroprotective Agent in a Common Carotid and Distal Middle Cerebral Artery Occlusion Model (Infusion Study) in Rats"
53 / B04117	RR 764-01736 / 9/30/91	2/13/92	C.S. Krcmarik et al "Plasma Phenytoin Concentrations During a Two-Phase Intravenous Development Toxicity Study in Rats With CI-982 (Ann Arbor Toxicology Study 1637)"
53 / B04117	RR 745-01898 / 11/14/91	2/13/92	G. Krishna "Mouse Micronucleus Study of CI-982"
62 / B04118	RR 745-01859 / 9/30/91	6/11/92	J. Petrere "Intravenous Dose Range-Finding Study in Pregnant Rats With CI-982"
62 / B04118	RR 745-01931 / 3/4/92	6/11/92	J. Petrere "Intravenous Teratology Study in Rabbits With CI-982"
62 / B04118	RR 764-01812 / 3/12/92	6/11/92	K. Buckley et al "Plasma Phenytoin (CI-73) Concentrations in Female Rabbits Following CI-982 Intravenous Administration on Gestation Days 6 Through 18 (Ann Arbor Toxicology Study 1642)"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author / Title
62 / B04118	RR 745-01935	6/11/92	D. Monteith "In Vitro Mutation Assay of CI-982 in V79 Chinese Hamster Lung Cells"
62 / B04118	RR 764-01821	6/11/92	K. Buckley et al "Plasma Phenytoin (CI-73) Concentrations in Female Rabbits Following CI-982 Intravenous Administration on Gestation Days 15 Through Lactation Day 20 (Ann Arbor Toxicology Study 1642)"
62 / B04118	RR 764-01827	6/11/92	K. Buckley et al "Plasma and Whole Blood Phenytoin (CI-73) Concentrations From Samples Collected During Week 2 of a 4-Week CI-982 Daily Repeated Dose Toxicity Study in Dogs (Ann Arbor Toxicology Study 1683)"
63 / B04119	RR 724-00162	6/11/92	W. Bovenkerk et al "A Double-Blind, Placebo-Controlled, Safety and Pharmacokinetic Study in Healthy Subjects of Intravenous Fosphenytoin (CI-982) and Intravenous Dilantin (Protocol 982-12)"
79 / B04120	RR 745-01958	10/12/92	M. Kropko "Standard AMES Bacterial Mutagenicity Assay of CI-982"
79 / B04123	RR-Memo 764-01828	10/12/92	K. Buckley et al "Plasma Phenytoin (CI-73) Concentrations in Male Rats on Study Days 0 and 73 Following Intramuscular Treatment With CI-982 (Ann Arbor Toxicology Study 1679)"
79 / B04123	RR-Memo 764-01826	10/12/92	K. Buckley et al "Plasma and Whole Blood Phenytoin (CI-73) Concentrations From Samples Collected During Week 3 of 4-Week CI-982 Daily Repeated Dose Toxicity Study in Rats (Sheridan Park Toxicology Study 1462)"
79 / B04120	RR 250-01648	10/12/92	R. Walker "Four-Week Daily Repeated Dose Intravenous Toxicity Study of CI-982 in Rats"
79 / B04120	RR 724-00159	10/12/92	W. Bovenkerk et al "A Double-Blind, Placebo-Controlled, Safety, Tolerance, and Pharmacokinetic Study of Intravenous Fosphenytoin (CI-982) and Intravenous Dilantin in Healthy Subjects (PR. 982-17)"

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	RR Date	Author / Title
79 / B04121	RR 745-01970 / 6/9/92	10/12/92	J. Reindel "Four-Week Intravenous Toxicity Study of CI-982 in Beagle Dogs"
79 / B04123	RR 740-03028 / 7/20/92	10/12/92	J. Goodrich "The Effect of the Anticonvulsants Fosphenytoin and Carbamazepine in the Gerbil BCO Model of Transient Global Forebrain Ischemia"
79 / B04121	RR 745-01973 / 8/18/92	10/12/92	J. Petrere "Two-Phase Intravenous Teratology Study in Rats With CI-982"
91 / B04124	RR 764-01908 / 1/6/93	3/4/93	K. Buckley/G.R. Loewen "Plasma Phenytoin (CI-73) Concentrations in Female Rats Following Intramuscular Treatment With CI-982 (Ann Arbor Toxicology Study 1760)"
97 / B05829	RR 745-02042 / 5/7/93	6/17/93	J.W. Henck "Intramuscular Fertility and General Reproduction Study in Male Rats With CI-982"
103 / B06147	RR 720-03148 / 6/8/93	7/15/93	B. Baron/A. Kugler et al "A 5-Day, Randomized, Double-Blind, Placebo-Contolled, Parallel-Group, Multicenter Clinical Study of Tolerance and Safety of Multiple Doses of Intramuscularly Administered Fosphenytoin Sodium (CI-982) Substituted for Oral Dilantin in Epilepsy of Neurosurg
105 / B06242	RR 745-02071 / 6/25/93	8/16/93	J.W. Henck "Perinatal-Postnatal Study in Rats With CI-982 Given Intravenously"
106 / B06329	RR 720-03224 / 7/19/93	9/22/93	B. Baron, et al "Open-Label, Multicenter Study of the Safety and Tolerance of Intramuscularly-Administered, Multiple-Dose Fosphenytoin in Hospitalized Neurosurgery Patients (Protocal 982-014)"
110 / B06376	RR 720-03255 / 8/30/93	10/22/93	B. Baron and L. Knapp et al "An Open-Label, Multicenter Study Assessing the Safety and Tolerance of an Intramuscularly Administered Loading Dose of Fosphenytoin (CI-982) in Patients Requiring a Loading Dose of Phenytoin (Protocol 982-022)"

SubType: IND

CI#: 982 | Sub Date: 3/31/86

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Product Name: Fosphenytoin Sodium Parenteral

Ser# Ref / Barcode	RR Number: / Sub Date	/ RR Date	Author / Title
110	RR 720-03256		B. Baron and L. Knapp et al
B06376	8/30/93	10/22/93	"A Double-Blind, Parallel-Group, Single-Dose, Multicenter Study Comparing the Safety and Tolerance of Intravenously Administered Fosphenytoin (CI-982) Versus Dilantin Parenteral in the Treatment of Patients Requiring a Loading Dose of Phenytoin (Protocol
110	RR 724-00191		M. Eldon
B06376	9/24/93	10/22/93	"A Dose-Ranging Tolerance Study of the Phenytoin Prodrug in Healthy Human Volunteers: A Single-Center Study"
110	RR 724-00192		M. Eldon
B06376	9/28/93	10/22/93	"Safety and Tolerance to Increasing Infusion Rates of ACC-9653 (Phenytoin Prodrug) Administered as a Bolus to Healthy Human Volunteers,"
113	720-03273		B. Baron and L. Knapp
B06734	9/23/93	1/21/94	"Evaluation of Phenytoin Levels After IM and IV ACC-9653 Administration in Epileptic Patients on Chronic Oral Dilantin Monotherapy (Protocol 9653-86-05 or 982-05)"
113	745-02109		R.M. Walker and J.R. Herman
B06734	10/19/93	1/21/94	"Assessment of the Potential Risk Associated with Exposure to Diphenylhydantoic Acid"
117	X-720-03182		D. Bailey, M. Eldon, et al.
	1/12/95	2/8/95	Investigator's Brochure: Cerebyx (Fosphenytoin Sodium Injection), (CI-982)

EXHIBIT 9
NDA LOG

FDA CONTACT

SubType: NDA

CI#: 982 | Sub Date: 7/14/94

Generic: | Appr Date:

Product Name: Cerebyx

SubType: NDA

CI#: 982 | Sub Date: 2/22/95

	Thu, Feb 10, 1994	Record of FDA contact: Obtain Cerbyx (fosphenytoin) NDA number.
	Denise - FDA J. Turner	The Cerbyx (fosphenytoin) NDA number is 20-450.
B06978	Thu, Feb 17, 1994	Record of FDA contact: NDA filing.
	J. Turner C. McCormick	Dr. Ed Fisher will be the pharmacology reviewer and Dr. Feeney will probably be the medical reviewer for the fosphenytoin NDA.
B06978	Wed, Mar 23, 1994	Record of FDA contact. Re: Determine status of FDA minutes of 1/16/92 and 3/8/9
	FDA - Chamberlain P-D - Turner	There are no FDA minutes of the January 1992 meeting. FDA will not have minutes of the March 1993 meeting available prior to our NDA submission.
B06978	Thu, May 19, 1994	Record of FDA contact. Re: Send PD a final copy of the abstract as sent to AAPS.
	P-D - Turner FDA - Hale	Dr. Hale mailed the attached note and abstract to me. She has also given Ms. Chamberlain a copy of the abstract for file.
B06978	Fri, May 27, 1994	Record of FDA Contact: Request extra copies of mutagenicity reports.
	P-D - Turner FDA - Fitzgerald	Dr. Fitzgerald requests that we send her abbreviated copies of previously submitted mutagenicity gene tox studies. She will review them prior to NDA submission to be certain that the studies conducted are adequate in light of the lack of carcinogenicity studies.
B06978	Fri, May 27, 1994	Record of FDA Contact: Request IND listings for mutagenicity studies.
	P-D - Turner FDA - Fitzgerald	In response to Dr. Fitzgerald's request, I instructed her as to where in the IND the mutagenicity gene tox assays were located (IND Ref. No. and date of submission).
B06978	Fri, May 27, 1994	Record of FDA Contact. Re: Determine NDA filing date.
	P-D - Turner FDA - Chamberlain	The NDA filing date is July 15. We do not need to provide computer disks of clinical studies for Biometrics, since there are no proof of efficacy studies. Nancy will follow-up on the need for computer disks of data for Biopharmaceutics.
B06978	Fri, May 27, 1994	Request extra copies of mutagenicity reports.
	Glenna Fitzgerald Janeth L. Turner	See hard copy in the Central Files. Non Worldwide Regulatory Affairs Contact.
B06978	Fri, May 27, 1994	Request IND listings for mutagenicity studies.
	Glenna Fitzgerald J. Turner	See hard copy in the Central Files. Non Worldwide Regulatory Affairs Contact.

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	Fri, May 27, 1994	Request IND listings for mutagenicity studies.
	Glenna Fitzgerald	See hard copy in the Central Files. Non Worldwide Regulatory Affairs Contact.
	J. Turner	
B06978	Mon, Jun 27, 1994	Determine if including IND Serial Number and submission date in the NDA Index woul
	Glenna Fitzgerald	Adding IND serial numbers to the NDA Index will not be helpful for the Cerebyx NDA. We should submit a desk copy of the Item 5 technical summaries with the NDA. At this time, FDA requests no additional mutagenicity studies for Cerebyx.
	Janeth L. Turner	
B06978	Tue, Jul 26, 1994	Confirm NDA receipt and identify CSO and other reviewers for the Cerebyx NDA.
	Robbin Nighswander	Robbin Nighswander will be the CSO, John Feeney the Medical Reviewer, and Ed Fisher the Pharmacology Reviewer. The other reviewers are not yet identified. The NDA has a receipt date of July 15, 1994. FDA requests 3 desk copies of NDA Volume 1.
	Janeth L. Turner	
B06978	Mon, Aug 01, 1994	Request 3 additional desk copies of volume 1 of the Cerebyx NDA
	Dr. Ray Baweja	Dr. Baweja requests 3 desk copies of NDA Volume 1.
	Janeth L. Turner	
B06978	Mon, Aug 22, 1994	See hard copy in Central Files.
	Nancy Sager	See hard copy in Central Files. Non Worldwide Regulatory Affairs Contact.
	Sean Brennan	
B06978	Mon, Sep 12, 1994	Inform of refusal to file for the Cerebyx NDA.
	Robbin Nighswander	FDA has refused to file the fosphenytoin NDA 20-450
	Janeth L. Turner	
B06978	Fri, Sep 16, 1994	Discuss our request for an informal conference as noted in FDA's NDA refusal to file l
	Robbin Nighswander	We should submit our pre-meeting material within the next 2 weeks to enable Robbin to more expeditiously set up a meeting to discuss FDA issues in the NDA refusal to file.
	Janeth L. Turner	
B06978	Tue, Sep 27, 1994	Discuss Cerebyx NDA Refusal to File
	Russel Katz, MD	
	Janeth L. Turner	
B06978	Tue, Sep 27, 1994	Discuss Cerebyx NDA refusal to file
	John Feeney	
	Janeth L. Turner	

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B06978	Tue, Sep 27, 1994 Robbin Nighswander Janeth L. Turner	Discuss Cerebyx NDA refusal to file.
B06978	Fri, Sep 30, 1994 Robbin Nighswander Janeth L. Turner	Inform FDA that the background material will not be available until the end of next w FDA was informed that we plan to send the background material on Thur, Oct 7. It should be Federal Expressed to the Woodmont address. If the meeting is at FDA, their conference room will hold no more than 8 - 10 Parke-Davis staff.
B06978	Thu, Oct 13, 1994 Robbin Nighswander Janeth L. Turner	Determine status of FDA review of our pre-meeting materials. The pre-meeting materials have been received and are being reviewed. Robbin will call me the middle to end of next week with potential meeting dates.
B06978	Tue, Nov 15, 1994 Robbin Nighswander Janeth L. Turner	Discuss NDA refusal to file meeting scheduled for December 8, 1994. The FDA refusal to file meeting is scheduled for December 8 from 1:30 to 3:30 in Washington. Dr. Leber will attend as will FDA medical and biopharmacuetics reviewers. It is not anticipated that any chemistry, toxicology, or animal pharmacology issues will be discussed. FDA will contact us if issues arise at their pre-meeting and we should bring representatives from these disciplines.
B06978	Tue, Nov 15, 1994 Ray Baweja Janeth L. Turner	Request desk copies of background meeting material submitted October 6, 1994. Representatives from Biopharmaceutics will be attending the December 8 refusal to file meeting and request 4 additional copies of our background meeting material (submitted to FDA on October 6, 1994.
B06978	Thu, Dec 01, 1994 Robbin Nighswander Janeth L. Turner	Discuss upcoming December 8 refusal to file meeting. A message was left on Robbin's voice mail indicating the PD meeting attendees and our plans to call him from the lobby prior to the meeting.
B06978	Thu, Dec 08, 1994 Robbin Nighswander Janeth L. Turner	Discuss logistics of NDA resubmission To reduce any potential for confusion while reviewing the NDA (where dose is expressed as phenytoin equivalents) and the package insert (where dose is expressed as fosphenytoin), the package insert in the re-submitted NDA will contain both the fosphenytoin and phenytoin equivalent dose. Robbin understands that we wish to use only the fosphenytoin dose in the final package insert. Robbin asks that I call him with an approximate re-submission date.
B06978	Mon, Dec 12, 1994 Tom Hassall Mary E. Taylor	User Fee User fee checks are deposited automatically therefore the only way a refund can be obtained is by a written request.

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B06978	Wed, Dec 21, 1994	Notify FDA of projected NDA re-submission date
	Robbin Nighswander Janeth L. Turner	The NDA will be re-submitted the 1st quarter of 1995. The logistics of the NDA re-submission will be discussed with FDA the first of January.
B06978	Mon, Feb 13, 1995	Clarify details for the NDA resubmission.
	Robbin Nighswander Janeth L. Turner	FDA asks that we provide one index in the updated NDA identifying the location of all documents in the July 1994 NDA and the updated NDA. The volumes in the updated NDA should be identified as 3.x. It is acceptable to provide only those clinical research report appendices that have been revised if it will significantly reduce the volume of paper submitted.
B06978	Wed, Feb 22, 1995	Ms. Wood called regarding the Cerebyx (resubmission) User Fee check sent to the Me
	Susan Wood Deborah Kiley-Marso	
B06978	Thu, Mar 09, 1995	FDA requests we FedEx 3 sets of volumes 3.1 and 3.8.
	Ray Baweja Byron Scott	FDA requests we FedEx 3 sets of volumes 3.1 and 3.8.
B06978	Wed, Mar 22, 1995	Request additional information/clarification from NDA
	G. Williams and R. M Janeth L. Turner	Biopharmaceutics requests specific data from the NDA in ASCII format, NONMEM data files, and a paper copy of specific appendices referenced in clinical Research Reports. (assigned Biopharmaceutics requests #1, 2, and 3)
B06978	Fri, Mar 24, 1995	Request additional clarification of March 22 Biopharmaceutics requests
	Dr. Raymond Miller Janeth L. Turner	Biopharmaceutics has Appendix D from 982-13. They do not request nonevaluable data until they have identified specifically what they need. They are most interested in receiving the ASCII and NONMEM data files as soon as possible.
B06978	Mon, Mar 27, 1995	Telephone conference call to discuss Biopharmaceutics requests of March 22, 1995.
	G. Williams/R. Miller Janeth L. Turner	The data provided in the NDA was clarified, as was the data currently available in ASCII and NONMEM format. The data not currently available in ASCII format is primarily the DuPont data. Since this data is low dose and rate of administration, it is not a high priority for Biopharmaceutics.
B06978	Fri, Mar 31, 1995	Determine if Biopharmaceutics has received our response to their requests and if they
	Dr. Raymond Miller Janeth L. Turner	Biopharmaceutics has received our response to their requests and our response appears fine. Dr. Miller has no additional requests at this time.
B06978	Thu, Apr 20, 1995	Discuss pharmacokinetics in Study 982-18.
	Ray Miller Stephen Olson/Alan	

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B06978	Wed, Apr 26, 1995	Determine status of NDA filing
	Robbin Nighswander	The Cerebyx NDA 20-450 is filed. The date of NDA receipt is 2/23/95. No possible Advisory Committee meeting dates have been identified.
	Janeth L. Turner	
B06978	Thu, May 18, 1995	Discuss FDA pharmacokinetic questions of April 20, 1995.
	Ray Miller/Gene Willi	
	Janeth L. Turner	
B06978	Thu, Jun 08, 1995	Request permission to include the Material Safety Data Sheet (MSDS) in the FOI versi
	Robbin Nighswander	FDA requests permission to include the MSDS in the FOI version of the EA. No additional information on the status of the NDA review is available.
	Janeth L. Turner	
B06978	Mon, Jun 26, 1995	Request desk copies from the NDA.
	Ray Baweja	Biopharmaceutics requests desk copies of specific NDA volumes to put into a team review project to expedite the NDA review.
	Janeth L. Turner	
B06978	Mon, Jun 26, 1995	Set up meeting to review interim results of fosphenytoin pharmacokinetic modeling.
	Ray Miller	An informal meeting with the Biopharmaceutics Division to discuss pharmacokinetic modeling will be held on July 14, from 9:00 am - 12:00 noon.
	Janeth L. Turner	
B06978	Tue, Jun 27, 1995	Finalize time of July 14 meeting.
	Ray Miller	The July 14 meeting will be from 8:30 am to 12 noon.
	Janeth L. Turner	
B06978	Wed, Jul 05, 1995	Determine possible timing for NDA 2nd Safety Update
	Robbin Nighswander	Information from study 982-26 should be submitted no later than October 23 to be reviewed and considered as part of an NDA approval prior to the February 23 user fee deadline.
	Janeth L. Turner	
B10119	Thu, Jul 13, 1995	To determine if a September advisory committee meeting is feasible.
	Paul Leber/Russ Katz	A September advisory committee meeting is not feasible. FDA has not yet determined if an advisory committee meeting will be necessary.
	Janeth L. Turner	

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B10119	Thu, Jul 13, 1995	Discuss positive in vitro mutagenicity test in pending NDA 20-450.
	Glenna Fitzgerald/Ed Janeth L. Turner	The positive mutagenicity study in the pending NDA should be in the Investigator's Brochure. Any repeat of this study or additional mutagenicity studies will be discussed via telephone conference call with Dr. Fitzgerald.
B06978	Fri, Jul 14, 1995	Review of Fosphenytoin pharmacokinetic modeling.
	Ray Miller Janeth L. Turner	Pharmacokinetic modeling is not an NDA review issue. It has aided in the understanding of fosphenytoin pharmacokinetics. Biopharmaceutics anticipates completing their NDA review this summer with a Biopharmaceutics Day in mid-September. To date, they have identified no Biopharmaceutics issues during their review.
B06978	Tue, Aug 01, 1995	Set up telephone conference call to discuss positive in vitro mutagenicity test in pend
	Glenna Fitzgerald Janeth L. Turner	The positive mutagenicity study is not an NDA review issue. It will need to be noted in the labeling. FDA is willing to discuss with us the design of any proposed future studies to help mitigate the labeling statement.
B10119	Thu, Aug 17, 1995	Request data from clinical biopharmaceutics trials for FDA NDA inspection
	Robbin Nighswander Janeth L. Turner	
B06978	Wed, Aug 23, 1995	To determine availability of method validation samples and to request submission of I
	Martha Heimann Sean Brennan	FDA requested that method validation section be submitted and samples be prepared for pick up by the Field Office.
B06978	Fri, Sep 01, 1995	Determine if FDA had received the clinical inspection documents requested on August
	Dr. C. T. Viswanatha Janeth L. Turner	Dr. Viswanathan has received the requested information. It is very feasible that he will conduct the inspections in September.
B06978	Tue, Sep 12, 1995	Request reformatting of Tables 5 & 6 in First (4-month) Safety Update
	John Feeney, MD Janeth L. Turner	The clinical review of the NDA is underway. Most of the questions should occur within the next six weeks.
B06978	Fri, Sep 22, 1995	Status of Advisory Committee for pending NDA
	Russel Katz, MD Irwin G. Martin, Ph.D	Division not planning for Advisory Committee for Cerebyx at this time.
B06978	Tue, Sep 26, 1995	Determine best way to inform FDA of a change in the fosphenytoin trade name.
	Robbin Nighswander Janeth L. Turner	We should submit a letter to the NDA noting our desire to change the trade name. Revised labeling does not need to be submitted at this time. A December Advisory Committee review of the NDA is not likely. Proposed revisions to the mutagenicity statement in the package insert should be submitted to the NDA.

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B10707	Wed, Oct 04, 1995	Schedule telephone conference call to discuss a possible error in fosphenytoin concen
	Ray Baweja Janeth L. Turner	Ray Baweja was not aware of the 483 received by Pharmaco. He must consult with Neuropharmacology before discussing with us how to handle correction of the fosphenytoin concentrations in the NDA.
B10707	Wed, Oct 04, 1995	Schedule telephone conference call to discuss a possible error in fosphenytoin concen
	Gene Williams Janeth L. Turner	Gene Williams was not aware of the 483 received by Pharmaco during FDA's inspection. Discussions on how to correct the fosphenytoin concentrations in the NDA need to be held with Ray Baweja. The Biopharm NDA review is scheduled to be completed by the first of November, with a Biopharm Day in mid-October.
B10707	Thu, Oct 05, 1995	Inform Robbin of my conversation with Biopharmaceutics concerning the error in the f
	Robbin Nighswander Janeth L. Turner	Left voice mail message informing Neuropharmacology that Biopharmaceutics would contact them concerning correcting the fosphenytoin concentrations in the NDA.
B10707	Wed, Oct 11, 1995	Determine how to work with FDA on correcting fosphenytoin concentrations in the N
	Ray Baweja Janeth L. Turner	Robbin Nighswander will be our FDA contact to determine how and what needs to be corrected in the pending NDA. A written explanation of the error would be helpful for FDA to identify the nature of the NDA corrections.
B10707	Thu, Oct 12, 1995	Determine how to modify the NDA documents to reflect the corrections in fosphenyt
	Robbin Nighswander Janeth L. Turner	Neuropharmacology has not determined how to best make the corrections to the NDA. In the meantime, they suggest that we proceed as we feel best. They suggest that all corrections be done so that the FDA Reviewer can readily see what has been corrected. All communication with FDA on these corrections should be through Robbin Nighswander.
B10707	Tue, Oct 17, 1995	Confirm that we are submitting a written explanation of the error in the fosphenytoin
	Ray Baweja/Gene Wi Janeth L. Turner	Discussions with FDA as to how to correct the fosphenytoin concentrations will occur after they have reviewed our written explanation.
B10707	Mon, Oct 30, 1995	Pre-approval inspection.
	Catherine V. Dabish Steven Samet	See hard copy in the Central Files. Non Worldwide Regulatory Affairs Contact.
B10707	Wed, Nov 01, 1995	Inform FDA of submission of second safety update and first corrected RR.
	Robbin Nighswander Janeth L. Turner	FDA was informed that the second safety update will arrive on November 1 and the first Research Report with the fosphenytoin corrections will be submitted later this week.
B10707	Thu, Nov 09, 1995	Determine the logistics for future submission of fosphenytoin concentration correctio
	Robbin Nighswander Janeth L. Turner	We should use our judgement on whether to provide complete reports or only the pages corrected. All corrections should be submitted to FDA prior to November 22. They have received the second safety update. No additional information is available on the Agency's reaction to our corrections to the fosphenytoin concentrations or on the status of the NDA review.

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B10707	Wed, Nov 15, 1995	Ascertain extent of concern on error in fosphenytoin levels in NDA
	Robbin Nighswander	There apparently is not a high level of anxiety over the error in fosphenytoin concentration calculations in the NDA if these are appropriately corrected. The impact of the other issues in the 483s remains unknown.
	Irwin G. Martin, Ph.D	
B10707	Thu, Dec 14, 1995	Fosphenytoin PAI Recommendation
	Catherine V. Dabish	See hard copy in the Central Files. Non Worldwide Regulatory Affairs Contact.
	Lori Urso	
B10707	Tue, Dec 19, 1995	Determine acceptable time-frame for submitting a revised package insert.
	Robbin Nighswander	To be considered in FDA's development of the package insert, a revised package insert should be submitted as soon as possible, and no later than the first week in January. The name Cerebyx is acceptable to the FDA's nomenclature committee, the suffix IM/IV is not acceptable. Drs. Leber and Temple will make a final ruling on the committee's recommendation as they prepare the NDA action letter. They are on schedule for a February NDA action letter.
	Janeth L. Turner	
B10707	Thu, Dec 21, 1995	Clarify dosing in 982-25 as listed in our IND annual report
	John Feeney, MD	The dosing for the 982-25 study in the annual report was erroneously reported as phenytoin equivalent doses - they are fosphenytoin doses. Dr. Feeney finds switching from fosphenytoin to phenytoin equivalent doses very confusing. He is considering recommending that the labeling be expressed as phenytoin equivalent doses to reduce the potential for confusion when switching patients to oral phenytoin.
	Janeth L. Turner	
B10707	Fri, Jan 05, 1996	Request references from second safety update.
	John Feeney, MD	Dr. Feeney requests copies of references #1, 3 and 5 in the second safety update.
	Janeth L. Turner	
B10707	Thu, Feb 08, 1996	FDA requests CRFs and lab listings for patient #982-022-004-011.
	John Feeney, MD	FDA requests more information concerning patient #982-022-004-011.
	Janeth L. Turner	
B10707	Thu, Feb 08, 1996	Determine status of NDA review.
	Robbin Nighswander	The NDA review is on schedule for a 2/23/96 action letter.
	Janeth L. Turner	
B10707	Fri, Feb 23, 1996	Alert to Approvable Letter status
	Robbin Nighswander	Cerebyx is approvable. Labeling to be updated; new section on comparison to Dilantin IV may be added.
	Irwin G. Martin, Ph.D	

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B10707	Tue, Feb 27, 1996	Clarification of FDA's February 23, 1996 approvable letter suggesting that we should
	Glenna Fitzgerald	
	Janeth L. Turner	

B10707	Wed, Feb 28, 1996	Determine procedure for submitting Cerebyx and Dilantin revised labeling.
	Robbin Nighswander	We should consider submitting the draft of the Dilantin labeling with the Cerebyx labeling. FDA's principal issue with expression of the dose as phenytoin equivalents was to convey to the physician that dosage conversion was not necessary, and that fosphenytoin can be given faster than phenytoin. It is doubtful that they will accept use of "mg" rather than "PE mg" when expressing the dose. We may submit to the NDA proposed revisions to the container and vial labels earlier than the revised package insert, but there is no guarantee that they will respond to this prior to action on the revised package insert. The information provided in the NDA was not adequate to support pediatric use. While FDA has 6 months to respond to our submission, they hope to do so much earlier than this.
	Janeth L. Turner	

B10707	Thu, Mar 14, 1996	To discuss response to the FDA approvable letter.
	Robbin Nighswander	FDA requests that we not submit the microbiology, stability, or Safety Update data until we submit our complete response to the approvable letter (to be submitted mid-April). Robbin is not aware of an FDA opinion on our June 1991 response to FDA's request to identify Dilantin as pregnancy category D. If still relevant, we should include a copy of this again in our current response to FDA.
	Janeth L. Turner	

	Tue, Mar 19, 1996	Inform FDA that we are submitting a report of a Dilantin 2-year rat carcinogenicity st
	Robin Pitts	Robin will continue to handle administrative matters for this IND. FDA was informed that the results of the Dilantin rat carcinogenicity study submitted on March 19 would be briefly mentioned in the revised Cerebyx package insert.
	Janeth L. Turner	

B10707	Fri, Mar 22, 1996	Inform of errors in March 14 Microbiology and CMC submission
	Robbin Nighswander	The errors will be corrected in our complete response to the approvable letter unless FDA calls and asks for them prior to this.
	Janeth L. Turner	

B10707	Mon, Apr 08, 1996	Determine status of March 13 submission regarding container and vial labeling and di
	Robbin Nighswander	Our response to the approvable letter will be treated as a major amendment and will restart the NDA review clock. FDA chemists are actively reviewing our March 13 labeling request, and while they will not have an official response until after they receive our complete response to the approvable letter, at this time they have no objections to our proposal. All NDA review copies, except Statistical, should be submitted, along with a WordPerfect electronic copy of the revised package insert and copies of all literature references. Pediatric labeling was discussed, but no final FDA opinion was conveyed.
	Janeth L. Turner	

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B10707	Mon, Apr 15, 1996	Review content and organization of our April 12 response to the NDA approvable lett
	Robbin Nighswander	
	Janeth L. Turner	

B10707	Wed, Apr 24, 1996	Request clarification of formate data submitted in our April 12, 1996 response.
	John Feeney, MD	The medical reviewer is actively reviewing our response.
	Janeth Turner	

B10707	Mon, Apr 29, 1996	Request clarification on origin of statement in revised package insert
	John Feeney, MD	FDA will make comments on the pediatric pharmacokinetic protocol as part of their response to our submission responding to their NDA approvable letter.
	Janeth L. Turner	

B10707	Tue, Apr 30, 1996	Request clarification on outcome of two patients with pruritis, in 982-27 RR memo.
	John Feeney, MD	Dr. Feeney requests information on the clinical outcome of two patients with pruritis in 982-27 RR memo.
	Janeth L. Turner	

B10707	Wed, May 01, 1996	Request additional information on Study 982-26
	John Feeney, MD	Dr. Feeney needs the results from Study 982-26, especially the adverse event listings.
	Janeth L. Turner	

B10707	Wed, May 01, 1996	Provide initial response to previous queries.
	John Feeney, MD	
	Janeth L. Turner	

B10707	Thu, May 02, 1996	Clarify request for additional information on Study 982-26
	John Feeney, MD	The adverse event listings will be submitted now. Once Dr. Feeney has reviewed these, he will let me know if he needs the complete report. He expressed a desire for narratives for specific adverse events in specific patients, but was not certain if it was necessary and will let me know if it is.
	Janeth L. Turner	

B10707	Fri, May 03, 1996	Request follow-up information from our May 2 submission.
	John Feeney, MD	Dr. Feeney requests all available information, including CRF for Center 7, Patient 8 and Center 10, Patient 1.
	Janeth L. Turner	

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B10707	Thu, May 09, 1996	Discuss status of review of our April 12 response to the approvable letter, specificall
	Robbin Nighswander	FDA hopes to have a response to our April 12 submission by the end of May. Our response to the approvable letter is actively under review by both Neuropharmacology and Biopharmacology. Discussions on including pediatrics in the labeling cannot take place until the Agency has determined their position. They will not have done this until they are ready to send us their response, which will include any proposed changes to the package insert.
	Janeth L. Turner	
B10707	Wed, May 29, 1996	Determine if FDA will complete their review of our response to the Cerebyx approvabl
	Robbin Nighswander	The FDA review will not be completed by May 31 because the medical reviewer is also reviewing a drug for ALS that is the subject of a June 7 Advisory Committee Meeting. Significant work on the Cerebyx review will not resume until after June 7.
	Janeth L. Turner	
B10707	Mon, Jun 17, 1996	Notify us of FDA revised draft package insert.
	Robbin Nighswander	Robbin will FAX me the revised package insert (attached). Once we have reached agreement on the package insert they will forward an approval package to Dr. Temple.
	Janeth L. Turner	
B10707	Tue, Jun 18, 1996	To understand why the strength (75 mg/mL) of fosphenytoin sodium is recommened
	Martha Heimann	Dr. Martha Heimann did not have comments on the submitted vial labels of fosphenytoin sodium and did not recommend adding the strength of fosphenytoin to the package insert.
	S. Brennan	
B10707	Wed, Jun 19, 1996	To provide information relative to discussion on product labels.
	Martha Heimann	The FDA did not provide comments on package labels because package insert revisions are still under discussion. Once the package insert is final, package labels will have to be revised accordingly.
	Sean Brennan	
B10707	Thu, Jun 20, 1996	Arrange teleconference to discuss labeling prior to submitting to FDA
	Paul Leber & Russ K	Dr. Leber is unwilling to hold a teleconference to negotiate final labeling, as this must be done with Dr. Temple. He is willing to review a FAX of revisions made at FDA's request and any corrections to the package insert.
	Janeth L. Turner	
B10707	Tue, Jun 25, 1996	FAX FDA potential revisions to the Package Insert
	Katura Higgins	The attached FAX was sent to Neuropharmacology at 12:00 (noon) Tuesday, June 25.
	Janeth L. Turner	

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B10707	Tue, Jun 25, 1996	Request additional information on protocols submitted to the IND (982-28, pediatric P
	John Feeney, MD	Dr. Feeney requests the randomization schedule and informed consent for Study 982-29. He offered comments on the 982-28 protocol, and we agreed that these would be discussed in more detail at a teleconference. Our rationale for revisions to the Precautions, Sensory Disturbances section and the Adverse Event Table 2 section of the package insert were discussed. He will review our faxed proposal, discuss them with Drs. Leber and Katz, and get back to me.
	Janeth L. Turner	
B10707	Wed, Jun 26, 1996	Determine status of FDA review of our FAX of June 25 with potential PI revisions
	Katura Higgins	Drs. Feeney, Katz, and Leber must review our response. Their review is not completed. Neuropharmacology will call me on Monday, July 1 if we have not heard from them prior to this.
	Janeth L. Turner	
B10707	Mon, Jul 01, 1996	Discuss proposed package insert revisions faxed to FDA on June 25, 1996.
	Mr R Nighswander/D	Revisions acceptable to FDA and those needing more discussion/review were identified. We will fax FDA additional revisions and supporting documentation for their review. Once FDA has responded to these, we will make a formal NDA submission of the container and vial labels and the package insert incorporating these revisions. Neuropharmacology will include this in an approval package to be forwarded to Dr. Temple for his review and signature.
	Janeth L. Turner	
B10707	Tue, Jul 02, 1996	Send FDA acceptable revisions and proposed revisions to the package insert, supporti
	Robbin Nighswander	The attached FAX was sent to Neuropharmacology at 12:00 noon, Tuesday, July 2, 1996.
	Janeth L. Turner	
B10707	Mon, Jul 08, 1996	Discuss logistics of our updated response to the NDA approvable letter.
	Robbin Nighswander	We should fax FDA our intention to include in the package insert the 10% rate of fetal abnormalities in epileptic women. The package insert in our updated response to the approval letter should be based on FDA's June 17, 1996 FAX.
	Janeth L. Turner	
B10707	Mon, Jul 08, 1996	To indicate acceptability of vial and container labels FAXed to FDA on July 2, 1996.
	Martha Heimann	The carton and vial labels as submitted in our July 2 FAX are acceptable with the Chemistry Reviewer. The decision to put the mg amount of fosphenytoin on the label was made by the Neuropharmacology medical reviewer, not the chemistry reviewer. Unless Dr. Temple disagrees, these will probably be the final approved labels.
	Janeth L. Turner	
B10707	Thu, Jul 11, 1996	Obtain information on Patient 8, Center 7, Study 26
	John Feeney, MD	The information requested was submitted May 8, 1996. Based on this, additional changes do not need to be made to the PRECAUTIONS, Sensory Disturbances portion of the package insert.
	Janeth L. Turner	

		SubType:	NDA
Cl#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
Cl#:	982	Sub Date:	2/22/95

B10707	Thu, Jul 11, 1996	Finalize package insert changes faxed to FDA on July 2.
	Mr R Nighswander/D	Based on our July 2 fax to FDA, all revisions noted as already meeting FDA approval are indeed acceptable, and all revisions submitted for review and discussion are acceptable with minor revisions. We should submit final labeling based on these revisions. Unless Dr. Temple makes additional changes, this will be the final approved labeling. The pediatric Phase 4 commitment and mechanism for FDA comment was discussed.
	Janeth L. Turner	
B10707	Tue, Jul 16, 1996	Discuss contents of July 12 response to NDA approvable letter.
	Robbin Nighswander	Because our July 12 response to the NDA approvable letter must have final sign-off by all FDA reviewers before it is sent to Dr. Temple, NDA approval by August 1 is probably not feasible. Biopharmaceutics is reviewing 982-28, and comments will be sent to us in the near future.
	Janeth L. Turner	
B10707	Tue, Jul 30, 1996	Request conference call to discuss revision in Phase IV commitment
	Robbin Nighswander	
	Janeth L. Turner	
B10707	Tue, Jul 30, 1996	Discuss Phase IV Commitment
	Mr R Nighswander/D	
	Janeth L. Turner	
B10707	Wed, Jul 31, 1996	FAX 7/30 meeting attendee list to FDA.
	Robbin Nighswander	P-D meeting attendee list from 7/30/96 teleconference was FAXed to FDA.
	Janeth L. Turner	
B10707	Mon, Aug 05, 1996	Inform us that the Cerebyx NDA is approved
	Robbin Nighswander	The Cerebyx NDA is approved.
	Janeth L. Turner	
	Mon, Sep 09, 1996	To check on the status of the review of Cerebyx launch materials.
	Lisa Stockbridge, Ph.	Comments on initial launch materials imminent.
	Patricia A. Carlson	

FDA CORRESPONDENCE

		SubType:	NDA
CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B07208		Wed, Jun 29, 1994	Initial Payment of User Fee for New NDA.
		FDA	As required for the Prescription Drug User Fee Act of 1992, please find enclosed a check (No. 312871) for $81,000 for a new drug application for Cerebyx (Fosphenytoin Sodium, Injection), NDA 20-450. This application contains clinical data
		B. McManus	
B07094	1	Thu, Jul 14, 1994	Original NDA.
		FDA	Pursuant to 21 CFR 314.50 enclosed is a New Drug Application (NDA) for Cerebyx® (fosphenytoin sodium) for use in the treatment of epilepsy. The NDA number for Cerebyx was preassigned on February 10, 1994.
		J. Turner	
B07208	2	Wed, Jul 27, 1994	Request for Desk Copy
		P. Leber	Attached, as per Mr. Robbin Nighswander's request of July 26, 1994, are three desk copies of Volume 1.1 of the Cerebyx® (fosphenytoin sodium) NDA 20-450, submitted to FDA on July 14, 1994.
		J. Turner	
B07208		Thu, Jul 28, 1994	Receipt of NDA.
		I. Martin	Letter acknowledging receipt (7/15/94) of NDA submitted 7/14/94.
		J. Purvis	
B07208		Thu, Jul 28, 1994	Acknolwedgement of receipt of NDA..
		I. Martin	Acknolwedgement of receipt of NDA.
		J. Purvis	
B07208		Mon, Aug 01, 1994	Request for Desk Copies
		R. Baweja	Attached as requested in your telephone call of August 1, 1994, are three desk copies of Volume 1 of the Cerebyx® (fosphenytoin sodium) NDA 20-450, submitted July 14, 1994.
		J. Turner	

		SubType:	NDA
Cl#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
Cl#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B07208	3	Fri, Sep 02, 1994	General Correspondence - Environmental Assessment
		P. Leber	Reference is made to NDA 20-450 for Cerebyx® (Fosphenytoin Sodium) Injection submitted on July 15, 1994. This correspondence provides for additional information requested by Ms. Nancy Sager on August 22, 1994 by telephone.
		S. Brennan	
B07208		Mon, Sep 12, 1994	Letter from FDA. Re: Application not acceptable for filing.
		I. Martin	On the basis of our initial review of you NDA, received on 7/15/94, and acknolwedged on 7/28/94, we have determined that the application is not acceptable for filing.
		P. Leber	
B07208	4	Wed, Sep 14, 1994	Informal Conference
		P. Leber	Reference is made to your September 12, 1994 letter regarding our New Drug Application (NDA 20-450) for Cerebyx® (Fosphenytoin Sodium) Injection, in which you stated you were refusing to file this NDA. As stated as an option in your letter, we request an informal conference about your refusal to file the Cerebyx Injection NDA.
		J. Turner	
B07208		Mon, Sep 19, 1994	Discussion with Paul Leber re: the Fosphenytoin NDA Refuse-to-File.
		R. Cresswell	Discussion with Paul Leber regarding the fosphenytoin NDA refuse-to-file. Paul agreed to a teleconference.
		W. Merino	
B07208	5	Thu, Oct 06, 1994	Background Material for Meeting
		P. Leber	Reference is made to your letter of September 12, 1994, notifying us of your refusal to file the Cerebyx® (Fosphenytoin Sodium) Injection NDA 20-450, and to my letter of September 14, 1994, requesting the informal conference noted in your September 12 letter.
		J. Turner	

SubType: NDA

Cl#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		

SubType: NDA

Cl#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B07208		Tue, Nov 15, 1994	Desk Copy of Background Material for Meeting.
		R. Baweja	Reference is made to the Cerebyx® (Fosphenytoin Sodium) Injection, NDA 20-450, and to the meeting background material submitted on October 6, 1994, in preparation for our December 8, 1994 meeting, to discuss FDA's September 12, 1994 refusal to file NDA 20-450. Attached as requested are 4 desk copies of the meeting background material submitted on October 6, 1994 (NDA Ref. No. 5). Please let me know if you need additional information in preparation for our December 8, 1994 meeting.
		J. Turner	
B07208	6	Fri, Dec 16, 1994	Minutes of December 8, 1994 refusal to file meeting.
		P. Leber	Reference is made to your letter of September 12, 1994, notifying us of your refusal to file the Cerebyx® (Fosphenytoin Sodium) Injection NDA 20-450; to the background refusal to file meeting material submitted to NDA 20-450 on October 6, 1994 (Ref. No. 5); and to our refusal to file meeting held on December 8, 1994. Attached are our minutes of the December 8, 1994 meeting. We would appreciate receiving any FDA comments on the attached minutes as well as a copy of FDA's minutes of this meeting as soon as they are available.
		J. Turner	
B07489		Fri, Feb 17, 1995	Payment of User Fee for Resubmission of New NDA.
		Mellon Bank	As required for the Prescription Drug User Fee Act of 1992, please find enclosed a check (No. 337770) for $104,000 for a resubmission of a new drug application for Cerebyx® (Fosphenytoin Sodium, Injection), NDA 20-450. This application contains clinical data. For information regarding this NDA submission, please contact: Janeth L. Turner Director, Regulatory Affairs Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road Ann Arbor, MI 48105 Telephone: 313/996-7426 FAX: 313/998-3283 An invoice for the second 50% of the application fee will be paid once the first action letter on the application is received by Parke-Davis.
		B. McManus	

		SubType:	NDA
CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B07456	7	Wed, Feb 22, 1995	Resubmission of Original New Drug Application (Volume 3.1 to 3.15).
		P. Leber	Reference is made to the Cerebyx® (fosphenytoin sodium) Injection NDA 20-450, submitted to FDA on July 15, 1994, and to FDA's letter of September 12, 1994 notifying us of their refusal to file this NDA. Reference is also made to the background refusal to file meeting material submitted to FDA on October 6, 1994 (NDA Ref. No. 4, Volume 2.1); to our December 8, 1994 meeting with FDA to discuss the refusal to file; and to our minutes of this meeting submitted to FDA on December 16, 1994 (NDA Ref. No. 6).
		J. Turner	
B07489		Fri, Mar 10, 1995	Request for Additional Copies
		R. Baweja	In accordance with your request during our telephone conversation on 3/9/95, three sets of Volume 3.1 and 3.8 are enclosed.
		J. Turner	
B07489	8	Wed, Mar 29, 1995	Response to Request for Additional Information
		P. Leber	Reference is made to the Cerebyx® (fosphenytoin sodium) Injection, NDA 20-450, submitted February 22, 1995 and to Dr. Raymond Miller and Dr. Gene Williams, Division of Biopharmaceutics, request of March 22, 1995 for additional information from this NDA. The following is provided to meet this request. The FDA requests are noted in italics followed by our response.
		J. Turner	
B07489	9	Thu, Jun 08, 1995	Environmental Assessment
		P. Leber	Reference is made to our pending Cerebyx NDA 20-450 and to Mr. Robbin Nighswander's, of your Division, request of June 8, 1995 to grant permission to allow FDA to include Attachment 2 of the complete Environmental Assessment (NDA Volume 3.4, pages 074 to 078) in the copy of the Environmental Assessment available under Freedom of Information (NDA Volume 3.7). Attachment 2 is the Material Safety Data Sheet. By copy of this letter we hereby grant you this permission.
		J. Turner	
B07489		Fri, Jun 16, 1995	Several deficiencies within the application
		I. Martin	Several deficiencies within the application which may be easily correctable. See File copy for complete letter.
		P. Leber	

SubType: NDA

CI#: 982 | Sub Date: 7/14/94

Generic: | Appr Date:

Product Name: Cerebyx

SubType: NDA

CI#: 982 | Sub Date: 2/22/95

Generic: | Appr Date:

Product Name: Cerebyx

B10119	10	Thu, Jun 22, 1995	First 4-Month Safety Update
		P. Leber	This submission updates the safety information for our pending NDA 20-450 for Cerebyx® (fosphenytoin sodium) Injection, filed February 23, 1995. The cut-off for the safety database is February 22, 1995. All deaths and serious adverse events are reported through May 15, 1995. This submission also updates the literature review for this pending NDA. The cut-off date for the literature review is March 10, 1995.
		J. Turner	
B10119	0	Mon, Jun 26, 1995	Request for Desk Copies
		R. Baweja	Attached as requested in our telephone conversation of June 26, 1995, are desk copies of the following volumes from the Cerebyx® (fosphenytoin sodium) Injection NDA 20-450: NDA Volumes 1.32, 1.33, 1.34, 1.35, 1.39, 1.42, 1.43, 1.46 submitted July 14, 1994; NDA Volumes 3.1 and 3.8 submitted February 23, 1995.
		J. Turner	
B10119	11	Fri, Jul 21, 1995	Responses to Deficient Letter Re CMC
		P. Leber	Reference is made to our pending NDA 20-450 for Cerebyx® (Fosphenytoin Sodium) Injection 75 mg/mL and to a communication of June 1, 1995 regarding deficiencies of Chemistry, Manufacturing and Controls Sections in the NDA. For convenience of review, the concerns and questions are repeated in italics followed by the response.
		S. Brennan	
B10476	12	Thu, Aug 24, 1995	Request for desk copies for clinical trial inspect
		C. Vishwanathan	Reference is made to the pending Cerebyx® (Fosphenytoin Sodium) Injection NDA 20-450 and to Mr. Robbin Nighswander's (Division of Neuropharmacology Drug Products) request of August 17, 1995, to send you the following materials from clinical Studies 982-14, 18, and 24: Study Report Protocol CRFs for all patients Analytical Reports This information is attached
		J. Turner	

SubType: NDA

CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		

SubType: NDA

CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B10493	13	Tue, Sep 05, 1995	NDA Amendment - CMC - Methods Validation Package
		P. Leber	Reference is made to our pending NDA 20-450 for Cerebyx® (Fosphenytoin Sodium) Injection 75 mg/mL and to a telephone request for validation samples and submission of an updated Item 4 (Samples and Labeling) of the NDA from the reviewing chemist, Dr. Martha Heimann of your Division on August 23, 1995.
		S. Brennan	

B10493	14	Thu, Sep 14, 1995	Requested Information
		P. Leber	Reference is made to the pending NDA 20-450 and to the First (4-months) Safety Update submitted June 22, 1995 (NDA Ref. No. 10). Reference is additionally made to Dr. Feeney's (Neuropharmacology Reviewing division) request of September 12, 1995 to reformat tables in this safety update. The following is provided to meet this request. The FDA request is noted in italics followed by our response:
		J. Turner	

B10493	15	Wed, Sep 27, 1995	Notification of proposed change in trade name
		P. Leber	Reference is made to the pending Cerebyx® NDA 20-450. We wish to change our proposed trade name as identified in this pending NDA from "Cerebyx®" to "Cerebyx® IM/IV". Modification in the draft labeling to reflect this proposed change will be made at the appropriate time in the NDA review process as requested by FDA.
		J. Turner	

B10846	16	Thu, Oct 19, 1995	Correction in Fosphenytoin Concentrations
		P. Leber	
		J. Turner	

B10846	17	Fri, Oct 27, 1995	Amendment - CMC
		P. Leber	Reference is made to our pending NDA 20-450 for Cerebyx® IM/IV (Fosphenytoin Sodium) Injection 75 mg/mL. The NDA is being amended to update the following Chemistry, Manufacturing and Controls sections of the NDA.
		S. Brennan	

SubType: NDA

CI#: 982 | Sub Date: 7/14/94

Generic: | Appr Date:

Product Name: Cerebyx

SubType: NDA

CI#: 982 | Sub Date: 2/22/95

Generic: | Appr Date:

Product Name: Cerebyx

B10846	18	Fri, Oct 27, 1995	Amendment: CMC Methods Validation Package
		P. Leber	Reference is made to our pending NDA 20-450 for Cerebyx® IM/IV(Fosphenytoin Sodium) Injection 75 mg/mL and to the Amendment (Reference No. 13; September 5, 1995) and to Item 4 (Samples and Labeling) of the NDA. As a result of the Amendment (Reference No. 17) submitted on October 27, 1995, we are revising Item 4. The validation samples requested by Dr. Martha Heimann were obtained at our Morris Plains facility by a representative, Mr. Anthony Crisuolo, of the Newark District Office on October 25, 1995.
		S. Brennan	
B10880	19	Tue, Oct 31, 1995	Second Safety Update
		P. Leber	Reference is made to the pending NDA 20-450, filed February 23, 1995, and to the First Safety Update, submitted June 22, 1995. Attached is the Second Safety Update to the pending NDA. The cut-off for the safety database is August 1, 1995. All deaths and serious adverse events are reported through September 15, 1995. This submission also updates the literature review for this pending NDA. The cut-off date for the literature review is August 17, 1995.
		J. Turner	
B10882	20	Fri, Nov 03, 1995	Correction to Fosphenytoin Concentrations
		P. Leber	Reference is made to our submission of October 19, 1995, (NDA Ref. No. 16) notifying FDA of an error in the fosphenytoin concentrations in our pending NDA 20-450.
		J. Turner	

		SubType:	NDA
Cl#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
Cl#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B12187	21	Mon, Nov 20, 1995	Correction to Fosphenytoin Concentrations
		P. Leber	
		J. Turner	

B12116		Wed, Dec 20, 1995	Detroit District Recommendation.
		L. de Vink	This letter is written to advise that the Detroit District has recommended to our CDER that the referenced NDA be approved, as a result of our 11/27-30/95 inspection. CDER will make their evaluation and notify PD accordingly.
		B. Holman	

B12116	22	Thu, Jan 04, 1996	Revised Package Insert
		P. Leber	Reference is made to the pending Cerebyx NDA 20-450 submitted on February 22, 1995. As discussed with Mr. Robbin Nighswander, attached are revisions to the draft Cerebyx package insert as submitted in our February 1995 NDA. The attached revised package insert does not contain or reflect any information not previously submitted to this NDA. These revisions are based on the safety information contained in the second safety update submitted October 31, 1995 (Ref. No. 19), and on our corrections to the fosphenytoin plasma concentrations as submitted November 20, 1995 (Ref. No. 21).
		J. Turner	

B12116	23	Mon, Jan 08, 1996	Request for Referencens from Second Safety Update
		P. Leber	Reference is made to the pending NDA 20-450 Cerebyx® IM/IV (Fosphenytoin Sodium) Injection 75 mg/mL, and to the Second Safety Update submitted October 31, 1995 (NDA Ref. No. 19). Attached as requested on January 5, 1996, by Dr. John Feeney, medical reviewer, are References 1, 3, and 5 as listed on Page 46 of the Second Safety Update.
		J. Turner	

B12116	24	Mon, Jan 08, 1996	CMC
		P. Leber	Reference is made to our pending NDA 20-450 for Cerebyx® IM/IV (Fosphenytoin Sodium) Injection 75 mg/mL, and to a telephone request by Dr. Martha Heimann of your Division on November 22, 1995, to perform a statistical analysis of the NDA stability data.
		S. Brennan	

SubType: NDA

CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		

SubType: NDA

CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B12116	25	Thu, Feb 08, 1996	Request for CRFs
		P. Leber	Reference is made to the pending NDA 20-450 and to Dr. Feeney's telephone request of today for copies of case reporting forms and laboratory values
		J. Turner	

B12116		Fri, Feb 23, 1996	Acknowledge Correspondence Receipt
		J. Turner	Please refer to your 7/14/94 NDA (and your resubmission dated 2/22/95). We acknowledge the following additional corresondence and amendments: September 2, 1994 July 21, 1995 October 31, 1995 September 14, 1994 September 5, 1995 November 3, 1995 October 6, 1994 September 14, 1995 November 20, 1995 December 16, 1994 September 27, 1995 January 4, 1996 March 29, 1995 October 19, 1995 January 8, 1996 June 8, 1995 October 27, 1995 February 9, 1996 June 22, 1995 (2 submissions) We have compelted the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to adopt as labeling for Cerebyx, the draft package insert attached to this letter, modified as requested.
		R. Temple	

B12116	26	Tue, Feb 27, 1996	Intent to File an Amendment
		P. Leber	We hereby notify you of our intent to file an amendment to this application containing a revised package insert and responses for information as outlined in the February 23 letter.
		J. Turner	

		SubType:	NDA
CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B13826	28	Wed, Mar 13, 1996	Review of Product and Container Labels
		P. Leber	Reference is made to the February 23, 1996, Cerebyx NDA 20-450 approvable letter. In that letter FDA made a number of requests for Parke-Davis' response. We are in the process of preparing a response to all of these requests. One of the requests was that we "revise all product and container labeling to appropriately convey that dosage conversion calculations do not need to be performed when converting patients between fosphenytoin and phenytoin (i.e., all labeling should clearly convey that 50 mg/ml of phenytoin is being delivered and that NO dosage conversion factor need be applied)." Because of the lead time necessary to prepare immediate container and carton labels prior to marketing, we are requesting FDA input to our response to this specific request prior to providing a response to all of FDA's requests.
		J. Turner	
B13826	27	Thu, Mar 14, 1996	Partial Response to Letter of 2/23/96 - CMC
		P. Leber	Reference is made to our pending NDA 20-450 for Cerebyx® Injection (fosphenytoin sodium) and to the letter from Dr. Robert Temple, M.D., Director of Office of Drug Evaluation I of February 23, 1996. Listed below are our responses to issues regarding Microbiology and Manufacturing and Controls. For convenience of review, the comments are repeated in italics followed by our response. (See file copy for list)
		S. Brennan	
B13826	0	Wed, Mar 20, 1996	General Correspondence: Meeting Minutes
		Central Labeling Co	Attached are the final minutes from the meetings held 3/6/96 and 3/8/96. The next meeting is scheduled on 3/27/96 from 8 - 10 a.m.
		I. Martin	
	29	Fri, Apr 12, 1996	Complete Response to NDA Approvable Letter
		P. Leber	Reference is made to our pending NDA 20-450, to FDA's February 23, 1996 NDA approvable letter, and to our letter of February 27, 1996 informing you that we intended to file an amendment in response to this approvable letter. The following information is provided as a complete response to the February 23, 1996 NDA approvable letter: (see file copy for additional information)
		J. Turner	

		SubType:	NDA
CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B14743	30	Wed, May 01, 1996	Response to Request for Additional Information	
		P. Leber		
		J. Turner		
B14743	31	Thu, May 02, 1996	Response to Request for Additional Information	
		P. Leber		
		J. Turner		
B14743	32	Thu, May 02, 1996	Response to Request for Additional Information	
		P. Leber	Reference is made to the pending NDA 20-450, FDA's February 23, 1996 NDA approvable letter, to our response to this approvable letter submitted April 12, 1996, and to Dr. Feeney's telephone call of May 1, 1996 requesting additional information, specifically the adverse event listing tables, from study 982-26. Attached are the following tables to meet this request. (see file copy for list)	
		J. Turner		

SubType: NDA

Cl#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
SubType:	NDA		
Cl#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B14743	33	Wed, May 08, 1996	Response to Request for Additional Information
		P. Leber	
		J. Turner	

B14743	34	Fri, Jul 12, 1996	Amendment - Updated Complete Response to NDA Approvable Letter
		P. Leber, M.D.	Reference is made to our pending NDA 20-450 for Cerebyx (fosphenytoin), to FDA's February 23, 1996 NDA approvable letter, to our April 12, 1996 response to this approvable letter, and to your June 17, 1996 fax of a revised package insert. Attached are the following documents: Attachment 1: Final printed labeling for the package insert incorporating all revisions as discussed with your Division. The revisions are highlighted in Attachment 3 and explained in Attachment 4. Fifteen copies of this final printed labeling are included in the archival copy of this submission. Attachment 2: A copy of the final printed container and vial labels for both the 2 mL and 10 mL vials. As with the final printed package insert, 15 copies of these labels are included in the archival copy of this submission.

B14743	35	Tue, Jul 30, 1996	General Coresspondence
		P. Leber, FDA	Reference is made to our pending NDA 20-450 Cerebyx® Injection (fosphenytoin sodium) and to our June 12, 1996 response to the NDA approvable letter. As per our July 30, 1996 teleconference with Mr. Nighswander and Dr. Katz of your Division, this letter revises the Phase IV commitment in our June 12, 1996 letter to read:
		J. Turner	

B14743		Mon, Aug 05, 1996	Approval of Application
		J. Turner	Application is approved.
		R. Temple	

		SubType:	NDA
Cl#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
Cl#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B14743	37	Tue, Aug 13, 1996	General Correspondence: Phase IV Commitment, Meeting Request, Change in Protocol
	P. Leber		Reference is made to the Cerebyx NDA 20-450 approval letter of August 5, 1996, which quoted our Phase IV commitment,
	J. Turner		
B21801	37	Mon, Aug 19, 1996	Advertising and Promotion
	P. Leber		Reference is made to the Cerebyx NDA 20-450 approval letter of August 5, 1996, which quoted our Phase IV commitment, '
	P. Carlson		
B21801	0	Mon, Aug 19, 1996	Advertising and Promotion
	L. Stockbridge		Reference is made to our NDA 20-450 for Cerebyx® (fosphenytoin sodium injection). Reference is also made to the Approval letter for this application, dated August 5, 1996, which requested submission of introductory promotional material for Cerebyx®. As requested, we are submitting two draft copies of each of the following promotional materials: (see file copy for list)
	P. Carlson		
B21801	38	Mon, Aug 26, 1996	Response to FDA Request - Final Printed Lebeling for Approved NDA 20-450
	P. Leber		Reference is made to the August 5, 1996, Cerebyx NDA 20-450 approval letter, requesting 16 copies of the FPL. Attached are 16 copies of the FPL inserted in plastic sheet protectors. As requested in the August 5, 1996, approval letter, a copy of the FPL has been submitted to the Division of Drug Marketing, Advertising and Communications along with our introductory promotional material on August 19, 1996 (Ref. No. 37).
	J. Turner		

		SubType:	NDA
CI#:	982	Sub Date:	7/14/94
Generic:		Appr Date:	
Product Name:	Cerebyx		
		SubType:	NDA
CI#:	982	Sub Date:	2/22/95
Generic:		Appr Date:	
Product Name:	Cerebyx		

B21801	39	Thu, Aug 29, 1996	Time Sensitive Patent Information
		P. Leber	Reference is made to our Cerebyx® (fosphenytoin sodium) Injection NDA 20-450. Please add the enclosed patent information to the Cerebyx NDA.
		J. Turner	

[redacted]

NDA RESEARCH REPORTS

SubType: NDA

CI#: 982 | Sub Date: 7/14/94

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Product Name: Cerebyx

SubType: NDA

CI#: 982 | Sub Date: 2/22/95

0		764-01736	C. S. Krcmarik, G. R. Loewen
	9/30/91	7/14/94	Plasma Phenytoin Concentrations During a Two-Phase Intravenous Developmental Toxicity Study In Rats With CI-982 (Ann Arbor Toxicology Study 1637).
0		740-02989	J. J. Cordon, P. A. Boxer
	10/3/91	7/14/94	The Effects of Fosphenytoin as a Neuroprotective Agent in a Common Carotid and Distal Middle Cerebral Arter Occlusion Model (Infusion Study) in Rats.
0		720-03148	Reviewed by: B. Baron, A Kugler, et al
	6/8/93	7/14/94	A 5-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Clinical Study of Tolerance and Safety of Multiple Doses of Intramuscularly Administered Fosphenytoin Sodium (CI-982) Substituted for Oral Dilantin in Epilepsy of Neurosurgery Patients (Protocol 982-013).
0		724-00191	
	9/24/93	7/14/94	A Dose-Ranging Tolerance Study of the Phenytoin Prodrug in Healthy Human Volunteers: A Single-Center Study.
0		720-03345	B Baron, L Knapp
	12/14/93	7/14/94	An Open Label, Multicenter Study Assessing the Safety and Tolerance of an Intramuscularly Administered Loading Dose of Fosphenytoin (CI-982) in Patients Requiring a Loading Dose of Phenytoin (Protocol 982-22).
0		720-03349	S Hankin, L Knapp, et al
	2/11/94	7/14/94	Report of an Ongoing, Open-Label, Rate Escalation, Multicenter Study to Access Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus (Protocol 982-016).
0		X 764-02148	P. J. Burger, A. R. Kugler
	4/26/94	7/14/94	Modeling the Pharmacokinetics of Fosphenytoin and its Conversion to Phenytoin in Healthy Subjects Receiving Intravenous Fosphenytoin (CI-982) and Intravenous Dilantin.
0		MEMO 764-02287	A. R. Kugler, S. C. Olson
	1/20/95	1/20/95	Cumulative Free Phenytoin AUC Analysis. Protocol 982-24.
1		764-01532	G. Loewen, H. Anhut
	11/1/90	7/14/94	Single and Multi-Dose Pharmacokinetics of Gabapentin (CI-945) in Epileptic Patients Maintained on a Constant Phenytoin Dose Regimen: Protocol 945-01.

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1		730-01974	Y. Huang
	1/18/91	7/14/94	Chemical and Radiochemical Purities of [14^C]CI-982 (American Critical Care ACC-9653) Synthesized by DuPont NEN.
1		744-00024	J.J. Miceli, J.R. Koup
	1/18/91	7/14/94	Study 982-01 (9653-86-01) A Dose of Ranging Tolerance Study of CI-982 in Healthy Volunteers: A single Center Study, 9653-86-01. Formate Level Appendices for RR 744-00024, dated 12/8/94 submitted 7/14/94.
1		744-00025	J. R. Koup, J. J. Miceli
	1/18/91	7/14/94	Absolute Bioavailability of Phenytoin After Intravenous CI-982 Administration of Healthy Male Volunteers, 9653-86-02.
1		744-00026	JJ Miceli, JR Koup
	1/18/91	7/14/94	Safety and Tolerance to Increasing Infusion Rates of CI-982 Administration as a Bolus Does to Healthy Volunteers, 9653-86-03.
1		744-00028	J. R. Koup, J. J. Miceli
	1/18/91	7/14/94	Absolute Bioavailability of Phenytoin After Intramuscular CI-982 Administration to Healthy Male Volunteers, 9653-86-06.
1		744-00029	J. R. Koup, J.J. Miceli
	1/18/91	7/14/94	Conversion of CI-982 to Phenytoin to Patients With Renal or Hepatic Disease Compared to Healthy Subjects-A Pilot Study, 9653-87-07.
1		744-00030	J. R. Koup, J. J. Miceli
	1/18/91	7/14/94	Absolute Bioavailability of Phenytoin From CI-982 in Patients With Therapeutic Serum Phenytoin Concentrations Using Stable Isotope Techniques, 9653-87-10.
1		744-00031	J.R. Koup, J.J. Miceli
	1/18/91	7/14/94	Evaluation of the Pharmacokinetic Interaction Between Diazepam and CI-982 in Healthy Male Volunteers.
1		764-01597	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94	In Vitro Hydrolysis of AC-9653 by Human, Dog and Rat Blood and Tissues.

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1			764-01598	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		HPLC/UV Assay of Phenytoin Prodrug in Whole Blood.
1			764-01600	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		Tissue Distribution Study of 14°C-ACC-9653 In Rats.
1			764-01601	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		Pharmacokinetic and Relative Bioavailability of Phenytoin After Intramuscular Administration of Phenytoin Sodium and ACC-9653 in Dogs.
1			764-01603	J. R. Koup, J.J. Miceli
	1/18/91	7/14/94		Standard Assay Procedure for HPLC Determination of Phenytoin in Blood.
1			764-01604	J. R. Koup, J.J. Miceli
	1/18/91	7/14/94		Standard Assay Procedure for HPLC Determination of Phenytoin Prodrug Blood.
1			764-01606	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		Pharmacokinetics and Bioavailabiltity of Phenytoin and Bioequivalence of ACC-9653 to Phenytoin Sodium After Intravenous Administration of ACC-9653 in Dogs.
1			764-01609	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		Pharacokinetics and Absolute Bioavailability if ACC-9653 and Phenytoin After Intravenous and Intramuscular Administration of ACC-9653 in Dogs.
1			764-01610	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		Comparative Pharmacokinetics and Bioavailability of Phenytoin After Oral Administration of Phenytoin Sodium Capsule and Intramuscular Administration of ACC-9653 in Dogs.
1			764-01611	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94		Distribution and Hydrolysis of Intramuscular ACC-9653 and Phenytoin Sodium.

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1		764-01612	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94	Determination of Blood Level of ACC-9653 and Phenytion in Rats After Intramuscular Administration of ACC-9653 or Phenytoin.
1		764-01616	JJ Miceli, JR Koup
	1/18/91	7/14/94	Simultaneous HPLC-UV Assay of Phenytoin and the Para- and Meta-Hydroxy Metabolites of Phenytoin in Dog Plasma and Urine.
1		764-01618	JJ Miceli, JR Koup
	1/18/91	7/14/94	Comparative Pharmacokinetics and Bioavailability of Phenytoin after Intramuscular Phenytoin Sodium, Oral Phenytoin Sodium, and Oral ACC-9653 in Dogs.
1		764-01619	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94	Single and Multiple-Dose Pharmacokinetics of Phenytoin and ACC-9653 After Simultaneous Intramuscular Administration of Phenytoin Sodium and ACC-9653 in Dogs.
1		764-01620	J. J. Miceli, J. R. Koup
	1/18/91	7/14/94	Plasma Protein Binding Interaction of ACC-9653 and Carbamazepine, Diazepam, Phenobarbital, Phenytoin, and Valproic Acid.
1		764-01623	J. R. Koup, J. J. Miceli
	1/18/91	7/14/94	Standard Assay Procedure for HPLC Determination of ACC-9653 in Human Urine.
1		764-01624	J. R. Koup, J.J. Miceli
	1/18/91	7/14/94	Standard Assay Procedure for Simultaneous HPLC Determination of Phenytoin, 5-(p-Hydroxyphenyl)-5-(Phenylhydantoin) (p-HPPH) and 5-(M-hydroxyphenyl)-5-Phenylhydantoin(M-HPPH) in Human Urine.
1		740-02904	F. W. Marcoux
	1/21/91	7/15/94	Comparative Study of the Effects of ACC-9653 and Phenytoin on Maximal Electroshock Seizures in the Mouse.
1		740-02905	F.W. Marcoux
	1/21/91	7/14/94	Comparison of the Antiarrhythmic Activity of ACC-9653 and Phenytoin in Cardiac Glycoside-Induced Arrhythmias In Vitro and in Vivo.

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1	740-02906		F. W. Marcoux
	1/21/91	7/14/94	The Comparative Plasma Levels and Hemodynamic Effects of High Dose Infusions of ACC-9653 and Phenytoin Sodium in Anesthetized Dogs.
1	740-02907		F. W. Marcoux
	1/21/91	7/14/94	Effects of ACC-9653 and Phenytoin on Guinea Pig Right and Left Atria.
1	740-02908		F. W. Marcoux
	1/21/91	7/14/94	Further Studies on the Effects of ACC-9653 and Pheytoin on Guinea Pig Atria.
1	745-01720		M. E. Lewandowski
	2/4/91	7/14/94	Acute Toxicity of ACC-9653 and Phenytoin in Neonate Rats by Intraperitonel Injection.
1	745-01722		M. E. Lewandowski
	2/4/91	7/14/94	Acute Toxicity of ACC-9653 and Phenytoin in Mice by 30-Minute Intravenous Infusion.
1	745-01723		M. E. Lewandowski
	2/4/91	7/14/94	Acute Toxicity if ACC-9653 and Phenytoin in Adult Rats by Intraperitoneal Injection.
1	745-01724		M. E. Lewandowski
	2/4/91	7/14/94	Comparison of the Venous and Perivascular Irritation of ACC-9653 and Sodium Phenytoin Formulation in Rabbits.
1	745-01725		M. E. Lewandowski
	2/4/91	7/14/94	Acute Toxicity of ACC-9653 and Phenytoin in Weanling Rats by 30-Minute Intravenous Infusion.
1	745-01726		M. E. Lewandowski
	2/4/91	7/14/94	Comparison of Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Rats by Bolus Injection.

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1	745-01727		M. E. Lewandowski
	2/4/91	7/14/94	Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin by 30-Minute Infusion in Rats.
1	745-01728		M. E. Lewandowski
	2/4/91	7/14/94	Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Beagle Dogs.
1	745-01729		M. E. Lewandowski
	2/4/91	7/14/94	Comparison of the Acute Intravenous Toxicity of ACC-9653 and Phenytoin in Beagle Dogs by 30-minute Infusion.
1	745-01730		R. W. Maher
	2/4/91	7/14/94	Seven Day Intravenous Dose-Ranging Study of ACC-9653 in CD Rats.
1	745-01731		R. W. Maher
	2/4/91	7/14/94	Seven Day Intravenous Dose-Ranging Study with ACC-9653 in Beagle Dogs.
1	745-01732		M. Blair
	2/4/91	7/14/94	Two Week Intravenous Toxicity Study of ACC-9653 in Rats.
1	745-01734		M. E. Lewandowski
	2/4/91	7/14/94	Determination of the Presence of Glucosuria After Intravenous Infusion of ACC-9653 and Phenytoin in Rats.
1	745-01736		M. E. Lewandoski
	2/4/91	7/14/94	Plasma Phenytoin Concentrations During a Two- Phase Intravenous Development Toxicity Study in Rats With CI-982 (Ann Arbor Toxicology Study 1637).
1	745-01737		M. E. Lewandowski
	2/4/91	7/14/94	Determination of the Local Irritation Effects of ACC-9653 and Phenytoin After Intramuscular Injection of Rabbits.

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1		745-01738	M. E. Lewandowski	
	2/4/91	7/14/94	Acute Toxicity of ACC-9563 and Phenytoin in Rats by Intramuscular Injection.	
1		745-01739	R. W. Maher	
	2/4/91	7/14/94	Fourteen Day Intramuscular Dose-Ranging Toxicity Study With ACC-9653 in Beagle Dogs.	
1		745-01741	M. E. Lewandowski	
	2/4/91	7/14/94	Determination of the Local Irritation Effects of ACC-9653 and Phenytoin After Daily Intramuscular Injection in Rabbits for Five Consecutive Days.	
1		745-01742	M. E. Lewandowski	
	2/4/91	7/14/94	Determination of the Maximum Tolerated Dose of ACC-9653 and Phenytoin by Intramuscular Injection in Dogs.	
1		745-01743	M. E. Lewandowski	
	2/4/91	7/14/94	Determination of Blood Levels of ACC-9653 and Phenytoin in Rats After Intramuscular Administration of ACC-9653 or Phenytoin.	
1		745-01744	R. W. Maher	
	2/4/91	7/14/94	13 Week Intramuscular Injection Toxicity Study of ACC-9653 in Rats.	
1		745-01745	R. W. Maher	
	2/4/91	7/14/94	Fourteen Day Intramuscular Dose-Ranging Study With ACC-9653 in CD Sprague-Dawley Rats.	
1		745-01746	M. E. Lewandowski	
	2/4/91	7/14/94	In Vitro Effect of an ACC-9653 Formulation and a Sodium Phenytoin Formulation on Human Blood.	
1		MEMO 745-01786	J. R. Herman, J. R. Koup	
	3/4/91	7/14/94	Assessment of the Potential Risk Associated with Systematic Formaldehyde.	

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1		764-01636	J. R. Koup, C.S. Krmarik, et al.
	6/4/91	7/14/94	Validated Liquid Chromatographic Assay for Fosphenytoin (CI-982) in Human Plasma.
1		740-02970	M.G. Vartanian, C. P. Taylor
	6/17/91	7/14/94	Effects of Fosphenytoin on NMDA-Medicated Neurodegeneration in Rat Pups.
1		745-01843	J. A. Petere
	6/18/91	7/14/94	Exploratory Intravenous Study in Rats with CI-982.
1		745-01844	J. A. Petere
	6/18/91	7/14/94	Exploratory Intravenous Study in Rabbits With CI-982.
1		764-01703	J. R. Koup, C.S. Kremarik, et al.
	7/17/91	7/14/94	Validated Liquid Chromatographic Assay for Fosphenytoin (CI-982) in Human Urine.
1		745-01733	M. Blair
	8/4/91	7/14/94	Two Week Intravenous Toxicity Study if ACC-9653 in Dogs.
1		745-01859	J. A. Petere
	9/30/91	7/14/94	Intravenous Dose Range-Finding Study in Pregnant Rats With CI-982.
1		745-01871	J. A. Petere
	9/30/91	7/14/94	Intravenous Dose Range-Finding Study in Pregnant Rabbits With CI-982.
1		740-02986	J.J. Cordon, M. E. Mann, Et al.
	10/3/91	7/14/94	Dose-Response Effects of Fosphenytoin in the Middle Cerebral Artery Occlusion (MCAO) Model of Focal Stroke in Rats.

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1		740-02988	J. Cordon, P. A. Boxer
	10/3/91	7/14/94	The Effects of Fosphenytoin on Infract Size and Neurological Deficits in a Proximal Middle Cerebral Artery Occlusion Model in Rats.
1		764-01773	K. A. Buckley, G. R. Loewen et al.
	11/1/91	7/14/94	Validated Liquid Chromatographic Assay for Phenytoin (CI-73) in Rabbit Plasma.
1		745-01898	G. Krishna
	11/14/91	7/14/94	Mouse Micronucleus Study of CI-982.
1		745-01931	J. A. Petere
	3/4/92	7/14/94	Intravenous Teratology Study in Rabbits With CI-982.
1		764-01812	K. A. Buckley, G. R. Loewen, et al.
	3/12/92	7/14/94	Plasma Phenytoin (CI-73) Concentrations in Female Rabbits Following CI-982 Intravenous Administration on Gestation Days 6 Through 18 (Ann Arbor Toxicology Study 1642).
1		764-01818	K. A. Buckley, G. R. Loewen, et al.
	3/19/92	7/14/94	Validated Liquid Chromatographic Assay for Phenytoin (CI-73) in Dog Plasma.
1		764-01819	K. A. Buckley, G. R. Loewen
	3/19/92	7/14/94	Validated Liquid Chromatographic Assay for Phenytoin (CI-73) in Rat Plasma.
1		764-01820	K. A. Buckley, G. R. Loewen, et al.
	3/19/92	7/14/94	Validated Liquid Chromatographic Assay for Pheytoin (CI-73) in Rat Whole Blood.
1		764-01823	K. A. Buckley, G. R. Loewen, et al.
	3/19/92	7/14/94	Validated Liquid Chromatographic Assay for Phenytoin (CI-73) in Dog Whole Blood.

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1		745-01935	D. K. Monteith
	3/24/92	7/14/94	In Vitro Mutation Assay of CI-982 in V79 Chinese Hamster Lung Cells.
1		764-01821	K. A. Buckley, G. R. Loewen
	3/24/92	7/14/94	Plasma Phenytoin (CI-73) Concentrations in Female Rats Following CI-982 Intravenous Administration on Gestation Day 15 Through Lactation Day 20 (Ann Arbor Toxicology Study 1686).
1		745-01958	M. L. Kropko
	4/9/92	7/14/94	Standard Ames Bacterial Mutagenicity Assay of CI-982.
1		764-01827	K. A. Buckley, G. R. Loewen, et al.
	4/24/92	7/14/94	Plasma and Whole Blood Phenytoin (CI-73) Concentrations From Blood Samples Collected During Week 2 of a 4-Week CI-982 Daily Repeated Dose Toxicity Study in Dogs (Ann Arbor Toxicology Study 1683)
1		764-01828	K. A. Buckley, G. R. Loewen, et al.
	4/30/92	7/14/94	Plasma Phenytoin (CI-73) Concentrations in Male Rats on Study Days 0 and 73 Following Intramuscular Treatment With CI-982 (Ann Arbor Toxicology Study 1679).
1		764-01826	K. A. Buckley, G. R. Loewen, et al.
	5/1/92	7/14/94	Plasma and Whole Blood Phenytoin (CI-73) Concentrations From Samples Collected During Week 3 of a 4-Week CI-982 Daily Repeated Dose Toxicity Study in Rats (Sheridan Park Toxicology Study 1492).
1		250-01648	R. M. Walker
	5/11/92	7/14/94	Four-Week Daily Repeated Dose Intravenous Toxicity Study of CI-982 in Rats.
1		724-00159	W. E. Bovenkerk, M. A. Eldon, et al.
	6/1/92	7/14/94	A Double-Blind, Placebo-Controlled, Safety, Tolerance, and Pharmacokinetic Study of Intravenous Fosphenytoin (CI-982) and Intravenous Dilantin in Healthy Subjects (Protocol 982-17).
1		724-00162	W. E. Bovenkerk, M. A. Eldon, et al.
	6/1/92	7/14/94	A Double-Blind Placebo-Controlled, Safety and Pharmacokinetic Study in Healthy Subjects of Intravenous Fosphenytoin (CI-982) and Intravenous Dilantin (Protocol 982-12).

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1		745-01970	J. F. Reindel
	6/9/92	7/14/94	Four-Week Intravenous Toxicity Study of CI-982 in Beagle Dogs.
1		745-01973	J. A. Petere
	8/18/92	7/14/94	Two-Phase Intravenous Teratology Study in Rats With CI-982.
1		764-01908	K. A. Buckley, G. R. Loewen
	1/6/93	7/14/94	Plasma Phenytoin (CI-73) Concentrations in Female Rats Following Intramuscular Treatment With CI-982 (Ann Arbor Toxicology Study 1760).
1		745-02042	J. W. Henck
	5/7/93	7/14/94	Intramuscular Fertility and General Reproduction Study in Male Rats With CI-982.
1		745-02071	J. W. Henck
	6/25/93	7/14/94	Perinatal-Postnatal Study in Rats With CI-982 Given Intravenously.
1		720-03224	B. Baron, A. Kugler et al.
	7/19/93	7/14/94	Open-label, Multicenter Study of the Safety and Tolerance of Intramuscularly-Administered, Multiple-Dose Fosphenytoin in Hospitalized Neurosurgery Patients (Protocol 982-014).
1		720-03273	B. Baron, L. Knapp
	9/23/93	7/14/94	Evaluation of Phenytoin Levels After IM and IV ACC-9653 Administration in Epileptic Patients on Chronic Oral Dilantin Monotherapy, (Protocol 9653-86-05 or 982-05).
1		724-00192	M. Eldon
	9/28/93	7/14/94	Safety and Tolerance to increasing Infusion Rates of ACC-9653 (Phenytoin Prodrug) Administered as a Bolus to Healthy Human Volunteers.
1		Memo 745-02109	R. M. Walker, J. R. Herman
	10/19/93	7/14/94	Assessment of the Potential Risk Associated with Exposure to Diphenylhydantoic Acid.

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1	764-02105		A. R. Kugler, S.C. Olson
	1/13/94	7/14/94	Method Validation and HPLC Analysis of Phenytoin in Human Plasma Ultrafiltrate (Pharmaco Analytical Laboratory Method LC99.1)
1	764-02106		A. R. Kugler, S. C. Olson
	1/13/94	7/14/94	Method Validation and HPLC Analysis of Fosphenytoin and Pheyntoin in Human Plasma (Pharmaco Analytical Laboratory Method LC108).
1	764-02107		A. R. Kugler, S. C. Olson
	1/13/94	7/14/94	Method Validation and HPLC Analysis of Phenytoin in Human Urine (Pharmaco Analytical Laboratory Method LC116).
1	764-02108		A. R. Kugler, S. C. Olson
	1/13/94	7/14/94	Method Validation and HPLC Analysis of Fosphenytoin in Human Urine (Pharmaco Analytical Laboratory Method LC115).
1	764-02109		A. R. Kugler, S. C. Olson
	1/13/94	7/14/94	Method Validation and HPLC Analysis of 5-(P-Hydroxyphenyl)-5-Phenylhydantion in Human Urine (Pharmaco Analytical Laboratory Method LC117).
1	764-02073		A. R. Kugler, S. C. Olson
	1/14/94	7/14/94	Stability of Fosphenytoin in Aqueous Solution and Blood Containing Either Heparin or EDTA as the Anticoagulant.
1	764-02096		L. L. Radulovic, H. N. Bockbrader
	1/31/94	7/14/94	Phenytoin Toxicokinetics in Male and Female Wistar Rats Following Single 150-mg/kg Fosphenytoin (CI-982) IM or IV Doses.
1	764-02110		AR Kugler, SC Olson
	2/2/94	7/14/94	Method Validation and HPLC Analysis of Fosphenytoin in Human Plasma Ultrafiltrate (Pharmaco Analytical Laboratory Method LC108.1).
1	720-03304		B. Baron, L. Knapp, Et al.
	3/10/94	7/14/94	A Double-Blind, Randomized, Parallel-Group, Multicenter Clinical Study if Tolerance and Safety of Multiple Doses of Intravenously Administered Fosphenytoin Sodium (CI-982) Verus Dilantin Parenteral in Neurosurgery Patients (Protocol 982-015).

SubType: NDA

CI#: 982 | Sub Date: 7/14/94

Generic: | Appr Date:

Product Name: Cerebyx

SubType: NDA

CI#: 982 | Sub Date: 2/22/95

1			744-00143	J. Besserer, J. Cook, et al.
	3/15/94	7/14/94		A Randomized, Double-Blind, Placebo- and Dilantin-Controlled, Single-Dose Study of the Pharmacokinetic and Tolerance Profiles of Intravenous Fosphenytoin Sodium (CI-982) in Healthy Subjects(Protocol 982-20-0).
1			744-00152	J. Besserer, M. Eldon, et al.
	3/25/94	7/14/94		A Randomized, Nonblind, Dilantin-Controlled, Single-Dose Study of the Pharmacokinetic Profile and Tolerance of Intravenous Fosphenytoin Sodium (CI-982) in Healthy Subjects (Protocol 982-24-0).
1			764-02074	A. R. Kugler, C. L. Webb, et al.
	4/4/94	7/14/94		Cross-Reactivity if Fosphenytoin in 2 Human Plasma Phenytoin Immunoassays.
1			744-00086	J Besserer, J Cook, et al
	4/23/94	7/14/94		A Randomized, Double-Blind, Placebo-Controlled, Rising Single-Dose Study of the Pharmacokinetic and Tolerence Profiles of Intravenous Fosphenytoin Sodium (CI-982) Administered at Five Different Infusion Rates to Healthy Subjects (Protocol 982-18-0).
1			764-02124	P. J. Burger, J. Cook, rt al.
	4/27/94	7/14/94		Characterization of Fosphenytoin and Phenytion Human Plasma Protein Binding in Vitro.
1			X 764-02114	P. J. Burger, J. A. Cook, et al.
	6/1/94	7/14/94		Pharmacokinetic Meta Analysis of Fosphenytoin Clinical Trials.
7			memo 764-02287	A. R. Kugler, S.C. Olson
	1/20/95	2/22/95		Cumulative Free Phenytoin AUC Analysis. Protocol 982-24.
7			720-03440	B. Baron, L. Knapp, et al
	2/10/95	2/22/95		Report of an Ongoing, Open-Label, Rate-Escalation, Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus (Protocol 982-016).

EXHIBIT 10
AGENCY LETTER

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U. S. Patent 4,260,769
Issued:	April 17, 1981
To:	V. Stella & K. B. Sloan
For:	5,5-DIPHENYLHYDANTOINS EXHIBITING ENHANCED SOLUBILITY AND THE THERAPEUTIC USE THEREOF

The Honorable Assistant Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

AUTHORIZATION OF AGENT AND POWER OF ATTORNEY

Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey and having its head office at One Merck Drive, P. O. Box 100, Whitehouse Station, NJ 08889-0100, being the owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint Warner Lambert Co., of Morris Plains, New Jersey, and the Attorneys named below:

Charles Ashbrook (Registration No. 27,610)
Francis Tinney (Registration No. 33,069)
Todd M. Crissey (Registration No. 37,807)

all being employees of Warner Lambert Co., individually and collectively to be the agents and attorneys of Merck & Co., Inc., with regard to an application for extension of the term of U. S. Patent 4,260,769 under 35 U.S. C. 156 and to transact all business in the U. S. Patent and Trademark Office in connection therewith.

Please address all communication in the above matter to:

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Merck & Co., Inc.

By: _____
Name: Joseph F. DiPrima
Title : Assistant General Counsel - Patents